BUREAU OF HYGIENE AND TROPICAL DISEASES.

TROPICAL DISEASES BULLETIN.

Vol. 27.] 1930. [No. 3.

MALARIA.

FAR EASTERN ASSOCIATION OF TROPICAL MEDICINE, TRANSACTIONS OF THE SEVENTH CONGRESS, BRITISH INDIA, 1927. Vol. 2. pp. 599–867. [**Malaria : Control (11 papers), General (10 papers), Treatment (9 papers).**]

The discussion on Malaria at this Congress was opened by Sir MALCOLM WATSON, who dealt with the methods employed by the Government of the Federated Malay States in the control of malaria. It is the policy of that Government that each land owner should be responsible for anti-malarial measures on his own land. In small holdings, towns, and villages, the Mosquito Destruction Boards, which have been set up in all districts, may assume the burden and recoup themselves by an assessment. The Government Railway is responsible for railway reservations, and the Mosquito Boards for all state lands. A Central Health Board has now been set up under the Health Board Enactment, with Local Boards in specified areas which submit to it recommendations for curative measures, such as hospitals and ambulances, the employment and payment of medical practitioners and attendance on estates, etc. ; it also submits schemes for preventive measures. The Central Board has power to impose a cess upon estates and mining lands in order to meet the cost of carrying out these recommendations.

Sir Malcolm Watson sees in the Health Board Enactment " nothing less than an attempt to wipe malaria out of Malaya," and he concludes that, " we shall press on, assured of great victory." He gave some interesting figures of the cost of anti-malaria work in Malaya. The upkeep of open drains and oiling, in intensely malarial hill land, costs about 30s. per hundred feet per annum. The capital cost of subsoil drainage is heavy in Malaya, but spread over twenty years it is less than one-third of the cost of oiling. " Quinine as a prophylactic has proved a complete failure."

Colonel S. P. JAMES read a short paper on anti-malaria measures for poverty-stricken regions in Europe, and on the recommendations of the Commission appointed by the Health Committee of the League of Nations. As an example of the problem which requires solution, he instanced malaria in Bulgaria, where two million penniless refugees have returned to their own country from Macedonia and elsewhere. He continued as follows : " Now it has to be admitted that, in circumstances of poverty such as those to which I refer, there is not, and perhaps never will be, enough money to apply the methods of malaria

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control which have proved effective in certain small and relatively wealthy areas in various parts of the world. No one doubts the efficacy of these measures when they can be thoroughly applied, but everyone agrees that they are difficult and very expensive." Col. James's actual words are given because his position is often misunderstood, and his views are often mis-stated. He pointed out that the Commission have not yet succeeded in finding a simple and cheap method of dealing effectively with the disease in poverty-stricken districts, and that, in the meantime, they recommend that the disease should be controlled, first, by the direct methods of treating the sick, which has robbed the disease of its importance in several European countries, and killing the mosquitoes in houses; and, secondly, by the indirect method of improving the economic and social conditions of the people. The object of "bonification" is " to change a poverty-stricken, sparse, scattered, often semi-nomadic, population into one which is settled and well to do, with proper arrangements for housing, water supply, education and general welfare, and with adequate medical attention. A change of this kind does not eradicate the causes of endemicity and the sources of malaria, but it quickly brings about a cessation of severe and fatal cases and a significant reduction of bad effects, so that the disease comes finally to be of little or no importance as a cause of sickness and death."

Dr. J. W. Scharff contributed a paper on the results of mosquito control in the rural areas of Singapore. *A. maculatus* is practically the only carrier of malaria, and the method adopted was its destruction in the larval stage. Paris green was found unsuitable, because: (1) it is difficult to handle in wet weather; (2) its invisibility when dusted on water makes supervision very difficult. Oiling was found to be expensive, supervision was a great tax on the responsible officer, the oil was heavy to carry and " coolies are always on the alert to pour oil in bulk down a drain, to relieve themselves of the unwelcome burden." The method adopted was a campaign of oiling dangerous breeding places within half a mile of each village, followed by a gradual extension of permanent drainage. The result has been " a steady improvement in the prosperity and health of the inhabitants;" in treated villages the spleen rate was reduced from 33 per cent. in 1921, to 5½ per cent. in 1927, while, in untreated control villages, there was no such reduction.

Colonel C. A. Gill expressed the opinion that no one acquainted with the condition in the Punjab during the malaria season could avoid the conclusion that men, money, and material were not available to control malaria by anti-larval measures. It was his experience that wherever poverty and scarcity of food prevailed malaria was hyper-endemic, although mosquitoes were not abnormally abundant. The ten million acres under canal irrigation in the Punjab constitute a vast bonification scheme which has improved the standard of living. In some areas, irrigation has been responsible for water-logging, but the Drainage Board is now engaged in dealing with this, and special attention is also being given to the removal of jungle-growth near human habitations. " Nothing is more striking in the Punjab," he said, " than the absence of relationship between the relative prevalence of anophelines and the local incidence of malaria and nothing is more conspicuous than the relatively high incidence of malaria in association with environmental conditions characterized by relatively high atmospheric humidity "; and measures designed to improve drainage and to prevent flooding, by reason of their influence upon atmospheric humidity, play an important part in reducing malaria.

Dr. C. STRICKLAND, as an illustration of the "species-control" of malaria, recounted the good effects of deliberately planting ribbons of jungle over drains where *A. maculatus* was breeding on a tea estate in Assam.

Colonel KATSUMI MATSUNO, Professor in the Army Medical College at Tokyo, spoke of the malaria in central Japan. Benign tertian is the only type and *A. sinensis* the only carrier. He had seen 735 cases in 20 years.

Colonel W. W. CLEMESHA gave an account of an outbreak of malaria on a healthy tea estate, about 3,000 feet above sea level, in Travancore. This outbreak occurred during the winter months, when the mean temperature is under 70° F. and the night temperature is frequently as low as 50° F. No mosquitoes breed in the neighbourhood at this season, nor would parasites be likely to develop in them if they did so. Colonel Clemesha attributed the outbreak to the presence of infected, hibernating mosquitoes (*A. culicifacies*) in cow-sheds situated near the coolie-lines. He mentioned several instances of attacks of malaria in Europeans which occurred before mosquitoes had become active in the spring, and he concluded that the only satisfactory explanation is that anopheles, some of which were infected during the previous year, awoke to activity early, and succeeded in infecting a number of human beings. Colonel Clemesha described the great difficulty of dealing with malaria on tea estates situated in the plains of Assam. The numerous collections of water, the high ground-water, the many species of anophelines, and the meteorological conditions, all favour malaria. The coolies live in houses built by themselves, scattered about the estates. There are usually many anopheline breeding places on the borders of the estates (such as rice-fields fed by mountain streams) which are not under the control of the management. He considered that a remedy would be the concentration of the labour force in suitable lines in the centre of the estates, but this involves great expense.

Mr. M. O. T. IYENGAR, entomologist to the Bengal Public Health Department, contributed a paper on the epidemiology of malaria in the Lower Bengal Delta in the neighbourhood of Calcutta. This area is flat, but the banks of the many rivers are raised, and between them are depressed areas which form natural basins. Malaria is hyper-endemic in the higher and drier areas near the rivers, but there is very little malaria in the low-lying land between them. The author's explanation is that *A. minimus* (*A. funestus*) breeds in the temporary collections of water left just after the monsoon in the high land, but is prevented from breeding at that season in the low lands because these are flooded. Later on, all the collections of water in the higher lands dry up and *A. minimus* disappears, but in the low lands the floods subside leaving pools in which the anophelines breed. Malaria, however, does not appear in these low lands because the season is too late for transmission. "The coincidence of the increase of the carrier anopheles with the transmission season marks an endemic area . . . the mere presence or absence of carrier anopheles is of no great material consequence."

Colonel S. P. JAMES, Mr. W. D. NICOL and Mr. P. G. SHUTE, of the British Ministry of Health, have been engaged for several years in preparing batches of infective mosquitoes for therapeutic use in mental diseases. Their practice is to collect about three hundred specimens of *A. maculipennis* in the adult stage, to feed them upon a suitable case daily, and to incubate them at 23° C. for about a fortnight until they become infective. They have found that there is a very high death

rate among the mosquitoes from April to July, and a very low death rate in other months, particularly from August to October. They have also found that the high death rate coincides with the season of maturation of the eggs and oviposition. They conclude that this is the cause of the high mortality, and that " in future, we must endeavour to correlate the seasonal incidence of primary malaria, not with the seasonal prevalence of the mosquito concerned, but with the seasonal prevalence of the individuals which live long enough to be transmitters." [Some of the statements in this paper are made rather ambiguous by a slip in a decimal point.]

Mr. SENIOR WHITE read a paper on the biological control of mosquito breeding. He and others have found that only extremes of pH have any inhibitory effect. In Ceylon, acidity other than that due to CO_2 is definitely prejudicial to breeding. In general, a low oxygen content is unfavourable to most species ; in rice-fields there is apparently a close relationship between rise in oxygen content and the entrance into the fields of the carrier species (*A. funestus*). Saline ammonia in higher quantity than 1 part per million inhibits all anophelines other than the *rossi* group. WILLIAMSON considers it probable that the true inhibitory effect is not ammonia *per se*, but the ammonia-nitrate ratio, and Mr. SeniorWhite suggests the insemination of breeding places with bacteriophages which destroy nitrifying organisms.

Professor K. B. WILLIAMSON believed that biological chemistry would throw light on the adaptation of mosquitoes to the water in which they are found, and on the adaptation of malaria parasites to their insect and human hosts. He considered it possible that some bacteria present in putrescent water may generate poisons which inhibit mosquito breeding. Many plants, such as *Euglena*, which grow only where pure-water-breeding mosquitoes are absent, are not themselves the cause of the absence of these mosquitoes, but the waters which suit them happen to be unsuitable for the mosquitoes. The mineral salts present in the water must be considered ; in Malaya, *A. maculatus* is present in granitic districts, and *A. karwari* takes its place in streams which flow through a laterite soil. Ferruginous waters are unfitted for anopheline larvae. Saline tolerance is not uncommon among malaria vectors, and *A. crucians* and *A. multicolor* apparently carry malaria only when they breed in salt water. The question arises if the malaria-carrying power of mosquitoes is identical when they are bred from waters of different degrees of purity ; the danger of certain species in some countries and their harmlessness in others may be explained on these grounds. Rotting vegetation prevents mosquito breeding in the rice-fields of some Malayan districts, and Professor Williamson considers that " there is the possibility of changing the anopheline fauna by regulating the amount and kind of organic matter in the water . . . species which breed in pure water, and among them at least many efficient vectors, should be the easiest to eradicate by a minimum of rot."

Mr. Bruce MAYNE stated that the inoculation of the contents of the stomach of a single *A. quadrimaculatus*, weighing 3 mgm., was sufficient to cause malaria. He was not able to transmit malaria direct from man to man by feeding mosquitoes on malaria patients and allowing them, immediately, to bite healthy persons, although he was able to find plasmodia in a saline suspension prepared from the macerated proboscis after the first feeding. When he fed infected mosquitoes on sterile dates, active sporozoites were found in suspensions made from the fruit.

Colonel S. R. CHRISTOPHERS expressed the opinion that both accurate splenometry and measured parasite counts (e.g., by Sinton's method, with fowl's corpuscles) are practicable in the field and are essential to the study of malaria. He demonstrated the method, used in India, of estimating the size of enlarged spleens by two measurements, one along a line drawn from the apex of the spleen to the umbilicus, and the other from the apex to the middle line. Tables were given showing the corrections of spleen measurements to be made in children of different ages and sizes. Major COVELL pointed out the advantages of Christophers's method as compared with the old method of measuring from the costal margin.

Dr. S. L. SARKAR gave an account of the development of immunity to malaria among the children of the Chittagong hill-tribes, as shown by the decrease in the size of their spleens after the age of three years, and by the intermittent type of their fever.

Major J. A. SINTON stated that he had come to the conclusion that the adult splenic index in a treated population is no true indication of the amount of uncured malaria; and that cured persons in an untreated population rapidly lose their enlarged spleens in the absence of re-infection. Colonel JAMES agreed that the splenic index was misleading in areas where quinine treatment is practised, and he had found it misleading in countries where malaria has a low endemicity and short seasonal prevalence.

Colonel S. P. JAMES, Mr. W. D. NICOL, and Mr. P. H. SHUTE presented a paper on the treatment of malaria, with special reference to the natural processes and the conditions which, without drug treatment, protect certain individuals from the ordinary symptoms and effects of a malarial infection. They found that about 25 per cent. of the patients who were bitten by mosquitoes carrying sporozoites failed to become infected; in others, the infection remained latent for six months or more before an attack occurred; in yet others, there was an abortive primary attack without discernible parasites in the blood, followed by an obvious attack months later. "At the time of their inoculation some natural process or artificial condition was at work which prevented the development of the malarial infection." Another interesting subject discussed by the authors was the development of immunity to a particular strain of benign tertian parasites, which follows its repeated inoculation. They found that persons thus immunized were readily infected by other strains of benign tertian, but the resulting attack was abortive. "The chief aim of experimental work should be to ascertain how to assist the physiological protective and curative processes which many individuals seemed naturally to possess." Nearly all failures "to take" happened during the winter months; cold weather seems to assist the natural curative processes. Exercise favours relapses. A single dose of 5 grains of quinine, given about the middle of an attack of therapeutic malaria, seems to set in motion some natural process of cure and causes the fever to cease almost at once; but the cure is not complete, for recrudescences occur. A single dose, even of 30 grains, has no effect if given during incubation. A single dose given in the middle of an attack must be as large as 5 grains, or thereabouts, but no better effect is obtained by giving a larger dose such as 10 or 20 grains. A return of fever and parasites within six weeks the authors call a "Recrudescence"; if the interval is longer than six weeks, they call it a "Relapse." Recrudescences are more frequent after relapses than after the primary attack, and it is considered probable that the causation of

relapses and recrudescences is entirely different. The authors conclude that thorough and prolonged quinine treatment is no more effective in preventing a relapse than the single small dose; but they are most emphatic in declaring that these conclusions apply only to the treatment of induced malaria in England, and that " it would be a great error to assume that the results obtained in England would be equally applicable to the treatment of malaria in tropical countries."

Major J. A. SINTON read a paper on the treatment of malaria with drugs. Among over fifteen hundred patients suffering from benign tertian malaria he has not found a single case of quinine resistance, although many of them arrived with histories of having this condition ; nor did he see relapses occur during the course of quinine treatment. The best results in the production of a permanent cure in malignant tertian malaria were obtained with quinine and alkali treatment. Fresh infections with *P. vivax* appeared to be more easily cured than chronic ones. The relapse rate in chronic benign tertian malaria was 60 to 70 per cent. Stovarsol and plasmochin caused a rapid disappearance of *P. vivax*. The relapse rate with stovarsol was about the same as that with quinine. The toxicity of plasmochin made it unsuitable in its present form for mass treatment in an uneducated tropical population.

Colonel H. W. ACTON and Colonel R. N. CHOPRA made a communication concerning the action of quinine. Recapitulating former work, they stated that : KING and ACTON showed that when one gram of basic quinine was taken by the mouth, the concentration in the blood did not rise beyond 1 in 150,000. Acton found that quinine base was ten times more powerful at pH 8 than at pH 6. Acton and Chopra showed that the concentration in the blood was higher when alkalies were administrated. They also showed that the concentration was greater in the mesenteric than in the peripheral blood vessels, and to this they attributed the good effect of quinine in the treatment of sub-tertian infections. SINTON showed the clinical benefit of giving alkalies with quinine. ACTON, CURGEL and DEWEY, found that though quinine has a powerful action on malaria parasites, it has a marked depressant action on the heart. (Dr. S. L. SARKAR, who has carried out experiments with the cinchona alkaloids under the auspices of the Indian Research Fund, stated, in the discussion on the treatment of malaria, that quinine is the only cinchona alkaloid which has no deleterious effects upon the heart.) The present authors found that cultures of *Paramoecium caudatum*, with a pH of 8 were killed by a concentration of quinine equal to 1 in 35,000 ; at 1 in 120,000, the multiplication was hindered and this effect was seen in dilutions up to 1 in 250,000. They considered that the sub-lethal concentration in the blood of man paralyses the movements of the young malaria trophozoites on the surface of the red blood cells, so that, being unable to enter the cells, they are swept off by the blood stream and die of starvation within the internal organs.

Dr. K. E. SURBEK, of Sumatra, drew attention to the importance of graduating the dose of quinine according to the weight of the patient. He recommended treatment for two days with sodium cacodylate, alternating with four to six days' treatment with quinine. He had found the administration of tincture of iodine useful in the treatment of enlarged spleens.

Dr. B. SHAHA pointed out that the dangerous lowering of the blood pressure which sometimes follows the intravenous administration of quinine, can be largely avoided by giving the drug in divided doses.

Dr. I. F. DE MELLO had treated several series of patients with the smalarina of Professor Cremonése, a colloidal preparation of mercury and antimony. He found it devoid of action on malaria parasites. Major SINTON'S experience of the drug was the same.

Dr. K. MORISHITA stated that all the residents in Formosa were compelled by law to undergo a monthly blood examination for malaria, and that the positive cases were treated with quinine. The parasite rate was only 2 or 3 per cent., but it had been the same for about ten years, and he did not consider that the method had been wholly successful. This he attributed to the missing of latent cases, and to lack of supervision in the administration of the quinine. He suggested that, as all latent cases give a positive urobilinogen test, all persons with a positive reaction should be treated with quinine.

MM. TRUONG-DINH-TRI, and TRINH-HUU-LOI of Tonkin, recommended the injection of strychnine for the purpose of provoking attacks in the detection of latent malaria.

The following Resolutions on Malaria were passed by the Congress :—

Resolution I.

" The Malaria Section of the Seventh Congress of the Far Eastern Association of Tropical Medicine are aware of many instances of a great increase in the incidence of malaria caused by the facilities given to mosquito reproduction by engineering works, either during construction or afterwards, due to the different conditions brought about. This Congress is of the opinion that plans for railways, canals, harbours and all similar engineering works likely to affect the conditions producing malaria should be submitted to the proper public health authorities and their sanitary engineers before being sanctioned by Governments.

Resolution II.

" As it has been represented that differences of opinion regarding the best method of controlling malaria sometimes cause doubt in the public mind and so may hamper the progress of anti-malarial work, this Congress takes the present opportunity to emphasize the fact that there is no single method of malaria control applicable to all conditions and all countries.

" Nevertheless, they consider that for towns, mines, plantations, large public works and similar aggregations of people, the control of the breeding-places of the malaria-carrying species of mosquito is a method which should be employed whatever other anti-malarial measures are put into force. Whenever possible this control should be effected by permanent works which eliminate entirely the sources of mosquito breeding.

" For wide rural areas, specially those with scanty, poverty-stricken populations, the first step in the control of malaria is adequate research, so that the conditions present may be ascertained and the best methods of control under the particular circumstances ascertained as a result of such research. Methods of prevention may here be of great variety and include drainage, flooding, jungle clearing, jungle preservation, bonification, the promotion of agriculture, improvement of housing and the general economic condition, education, etc., of the people. The systematic killing of infected adult mosquitoes, screening, the use of anti-malarial drugs and a host of special methods have each also to be considered in their proper application. The Congress desires to stress the need not only of thoroughly trained malaria research officers, but of expert malarial engineers in whichever type of malaria prevention is at stake."

W. Fletcher.

United Fruit Company, Boston, Mass. Seventeenth Annual Report. Medical Department. 1928. Section II. pp. 34–123. With 2 graphs. [2 refs.] [**Malaria.**]

The main interest of the section of this report, which deals with malaria, centres in the accounts of an attempt to destroy the gametocytes in the blood of the population by the administration of plasmoquin on a large scale, and so to control malaria by rendering the infection of mosquitoes impossible. As the result of their investigations in the Panama division of the United Fruit Company, which have been reviewed already in this *Bulletin* (Vol. 26, p. 939), Barber, Komp, and Newman came to the conclusion that a very small dose of plasmoquin compound, consisting of 0·01 gram of plasmoquin and 0·125 gram of quinine, would prevent mosquito infection; and Dr. Otto Brosius reports that, during 1928, mosquito control was almost entirely disregarded in order to test the value of the gamete-destroying power of plasmoquin compound as a sanitary agent; for, as he writes, "much should be expected from treatment alone, assuming that quinine destroys the asexual parasites and plasmoquin the gametes." A complete survey was made of the camps and farms on the Panama Division, after which all those persons whose blood contained malaria parasites were subjected to treatment. The daily dose was 0·06 gram of plasmoquin and 1·75 grams (27 grains) of quinine. The patients were given 4 days' treatment to take at home; on the fifth day, their blood was re-examined and an additional four days' treatment was supplied; finally, they were instructed to take "tonic tablets," containing quinine, arsenic, and iron, for eight days more. The number of persons examined in the preliminary survey was 3,765; 477, or 12·67 per cent., of them were found positive, but only 375 received a complete course of treatment. None showed evidence of intoxication attributable to the drug. A second survey was made a few months later in order to estimate the effect of the treatment in reducing the amount of malaria; the result was disappointing: 2,176 persons were examined and 314, or 14·43 per cent., were found positive, an increase of 1·76 on the percentage found positive before treatment. A third survey was made later by Dr. Barber and his colleagues with results which were even more disappointing, for the rate of infection showed a still further increase, and of 1,045 persons examined, 22·48 per cent. were found to be infected with malaria parasites.* In view of

* The author calls this "a crucial test" of plasmochin and quinine as "a sole sanitary agent" and their failure in this respect is implied. The so-called test is far from satisfactory. First, there is no evidence that the 314 found positive at the second examination and the 235 at the third were new infections; they may well have been really positive at the earlier examinations or they may not have been examined before. Out of 5,941 persons examined in the first and second surveys only 1,387 persons were known to have been examined at both. Secondly, even if it be granted that they were new infections, they provide little support for the view that the plasmochin and quinine failed. Such a view assumes that all, or at least most, of the sources of infection were submitted to the drugs under test. But nearly a quarter of the positives received partial treatment or none, and the author himself subscribes to the view that blood examination only reveals about half the true infestation rate, so that many other infected and potentially infective persons must have escaped treatment.

It is to be noted too that the populations examined in the three surveys were by no means the same, the numbers examined at each farm or camp differing widely from one survey to the next in many instances, and the three surveys were done at different seasons of the year.

There is some evidence that plasmochin (as given) does not always sterilize in the fact that 33 positives treated after the first survey were positives at the second.

J. F. C. H.

the failure of treatment as the sole anti-malarial measure, strenuous efforts are now being made to inhibit the breeding of anophelines near towns and camps, and to destroy adult mosquitoes in the houses. In addition, mass, or "blanket," treatment with plasmoquin and quinine is being carried out, but it is impossible to treat everyone because there is no way of compelling the people to accept treatment. [This appears to be an insuperable obstacle to the sterilizing of populations by means of drugs. It will be noted that only about four-fifths of the infected persons on the Panama Division completed the full course of treatment, and the fact that none of them showed any toxic symptoms makes it appear doubtful if the full doses were taken by all those who were supposed to have done so.]

Patients in hospital were successfully treated with plasmoquin and quinine; Dr. Wilhelm CORDES treated all the malaria patients admitted to the Company's hospital at Preston, Cuba, with 0·04 gram of plasmoquin and 1·8 grams of quinine daily. He considers that plasmoquin is not to be compared with quinine as a clinical remedy, and that as "the importance of plasmoquin lies almost exclusively in its effects on the sexual forms of the parasites, its routine use should be considered for prophylactic rather than for curative purposes."

The Report contains many other papers of interest, among which are the following: Dr. W. E. DEEKS, the general manager of the Medical Department, reviews the methods of malaria control which have been adopted, and sets out the results. He points out that "to attempt to control malaria by the prevention of mosquito breeding alone, in the extensive areas under cultivation (over 7,000 square miles), even if practicable, would involve expenditure that no commercial organization would sanction." The chief measures adopted on the Company's plantations are "a short-radius control," or anti-larval measures around habitations; agricultural drainage by canals known as "drag-line ditches"; whitewashing the interiors of the houses, and destroying the adult mosquitoes within them; the screening of certain houses; treatment with plasmoquin and quinine. Dr. DEEKS gives the following figures as the results: In 1925, the malaria rate per 1,000 employees was 239; in 1926, it was 211; in 1927, it was 147; and in 1928, it was 100.

Dr. Manuel ROJAS reports on the treatment of pernicious malaria, accompanied by coma or convulsions, in the hospital at Limon, Costa Rica. It consists of intravenous injections of 1 gram of quinine bihydrochloride dissolved in 10 cc. of normal salt solution. Three minutes is occupied in giving each of the injections, they are administered twice a day for two or three days, or until the patient is able to take plasmoquin and quinine by the mouth.

Dr. THONNARD-NEUMANN administered 5 to 8 cc. of blood, containing subtertian parasites, to a series of six West Indian negroes who were suffering from diseases of the nervous system. In four cases, the malaria ran its course without fever; in two cases, there was a febrile reaction which lasted only 2 or 3 days; and, in all but one, the parasites showed a tendency to disappear spontaneously. The Editor of the Annual Report concludes that the negro race has apparently developed a high tolerance to malarial infection.

The Report contains a progress report by Dr. Eugene WHITMORE who is investigating blackwater fever. Laboratory tests were made in blackwater fever cases, in cases of malaria in blackwater subjects,

and in controls suffering from malaria. The following are the results : (*a*) The Kahn test for syphilis was not more often positive in thirteen cases of blackwater than it was in the controls. (*b*) There was no alteration of the coagulation time. (*c*) Resistance to hypotonic salt solution, saponin, and cobra venom was unaltered. (*d*) The serum of the blackwater patients showed no difference from the serum of the controls in its action on the patient's red cells, or on normal cells. (*e*) There was no indication that quinine bihydrochloride, in a dilution of 1 in 2,000, exerted any haemolytic action, either in mixtures of serum and red cells, or in mixtures of red cells and salt solution. In two convalescent cases, 0·2 cc. of a 1 in 1,000 solution of quinine were injected intradermally without causing any reaction. (*f*) The alkali reserve was measured in two cases, with the result that a slight degree of acidosis was found in both of them, but it was not more than that which is sometimes found in the routine examination of medical students in Washington. Dr. WHITMORE reviewed the sarcolactic acid hypothesis of BLACKLOCK and MACDONALD, and concluded that if acidosis is a factor in the production of haemolysis, it can only be additional to some other specific factor, since by no means all cases of excessive exercise (in which the lactic acid in the blood may be increased nine-fold), or of acidosis, no matter how severe, suffer from haemoglobinaemia or haemoglobinuria.

Under the heading of Malaria Parasite Surveys, Dr. BARBER, Mr. W. H. KOMP, and Mr. B. M. NEWMAN, of the Public Health Service, draw attention to the inadequacy of conclusions based on a single survey (see also IYENGAR, in this issue). In one of the Panama camps they found 46 per cent. of the inhabitants positive for parasites ; but when they made a second survey 19 days later, they found that positives were as numerous among those who were previously negative as among those who were previously positive. They concluded that when a single survey gives as high a rate as 46 per cent. it may be fairly presumed that all, or nearly all, of the population, is infected. Their investigations of the breeding places of *A. albimanus* (the chief carrier in Central America) convinced them that it is capable of adapting itself to a great variety of breeding-places which vary with changes in the weather. The found that the favourite breeding-places were collections of fresh or brackish water, open to the sun and not fouled by much decaying vegetation. In wet weather, they discovered it breeding in grassy depressions in the meadows, in ditches, in pools, and in animal tracks. They caught large numbers of adults in the houses of the labourers, and they emphasize the value of the adult anopheline index in assaying the value of antilarval measures.

W. F.

INDIAN MEDICAL GAZETTE. 1929. Oct. Vol. 64. No. 10. pp. 573–577.—**The Parasitology of Indian Malaria : Unpublished Information** [R. K.]

Major SINTON, the director of the Malaria Survey of India, has recently compiled a " Bibliography of Malaria in India " as the result of two years' search into the archives of various government departments. This will shortly be issued as the first number of a new publication entitled " Records of the Malaria Survey of India" [see below]. The editor of the *Indian Medical Gazette*, Colonel KNOWLES, has scrutinized most of the documents catalogued in the Bibliography ; " the informa-

tion which they contain covers India from north to south, and east to west, and constitutes a mine of entirely untapped information with regard to the epidemiology of Indian malaria." Only 15 per cent. of the catalogued papers have been published in journals, and 70 per cent. have never been printed. One of the many examples given is a report which exists only in manuscript form, by Lieut.-Col. H. STOTT, I.M.S. on a two years' survey of the Tochi Valley, dealing with malaria in a barren, mountainous country. It is very fully mapped and illustrated with magnificant photographs. " The outside world may think that malaria has been but little studied in India since Sir Ronald Ross . . . but the true facts are entirely different . . . The Malaria Commission of the League of Nations is at present touring India . . . We believe that they will be amazed at the amount of anti-malarial work and organization that is going on all over India ; . . . probably there is more investigation of malaria going on in this country than in any other in the world, when the funds available are considered." Col. KNOWLES is about to publish the parasitological information which he has gleaned from these unpublished papers ; " but there is a whole wealth of general epidemiological information in these reports which should be surveyed, edited and published." Col. KNOWLES mentions, incidentally, that there is an admirably conducted class for malariologists at Kurnal, under the auspices of the Malaria Survey of India, where he thinks that they can be much better trained for the work of the country than in England.

W. F.

SINTON (J. A.). **A Bibliography of Malaria in India.**—*Records of the Malaria Survey of India.* 1929. Oct. Vol. 1. No. 1. pp. 1–200. Calcutta : Thacker, Spink & Co. [Rs. 7–12 or 10s. 4d.]

Volume 1, No. 1 of the *Records of the Malaria Survey of India,* recently issued by the Indian Research Fund Association, consists of the " Bibliography of Malaria in India," referred to in the preceding summary. Major J. A. Sinton, the compiler, states that he originally intended only to gather together as many references as possible to the work done on malaria in India, but that, because of their close connexion with malaria, he has included also references to blackwater fever, and to works dealing with the Anopheline mosquito. Besides making systematic search for references in better known journals published mainly within the last 30 years, Major Sinton has paid especial attention to the valuable observations on malaria which lie hidden away in local and provincial publications in India and to the many manuscript reports buried in the files of various offices of which the ordinary worker has no cognizance. The bibliography is divided into five parts. Part 1 gives references to books and papers in journals ; Part 2 refers to published and manuscript reports prepared for the Central and Provincial Governments of India, and to military and other reports ; and Parts 3 to 5 form full subject, authors, and geographical indices to the 2,200 or more references given in Parts 1 and 2. The 42-page subject index which forms Part 3 is indeed far more than a simple index based on the titles of the various papers listed in Parts 1 and 2. It is an attempt to index in some detail the principal points dealt with in the actual texts of the papers. The section dealing with drug treatment, for example, has been divided up under 43 sub-heads, such as " Adrenalin," " Alkalies," " A-malariin," " Amylopsin," " Antimony,"

" Arsenic," etc., while under the Quinine entry, which itself covers three and a half pages, are given 42 sub-divisions such as " Absorption of," " Action on malaria parasites," " Adulteration," " Administration, methods of," " Blood concentration of," " Cost of," " Deterioration of," " Distribution of," and so on. The Bibliography should be invaluable to all who are concerned with malaria problems, and particularly to those engaged in malaria work in India.

R. L. S.

Sur (S. N.) & Ghosh (Banamali). **A Malaria Survey of Madarihat and its Environs.**—*Indian Med. Gaz.* 1929. Oct. Vol. 64. No. 10. pp. 558–561. With 1 sketch map.

The object of this paper is to show the importance of a mosquito survey before launching a scheme to reduce malaria :—

In order to improve the health of the small town of Madarihat it was proposed to connect all the borrow pits along the railway line and drain them into the nearest river. A timely survey made by the authors showed that no dangerous mosquitoes bred in the pits, but that the source of the malaria lay in the old bed of a diverted river where they discovered *A. culicifacies*, *A. listoni*, and *A. maculatus*.

W. F.

James (S. P.). **Remarks on Malaria in Kenya.**—*Kenya & East African Med. Jl.* 1929. July. Vol. 6. No. 4. pp. 92–98.

Col. S. P. James has recently completed a malaria survey of Kenya, and during his stay in that country, he addressed the local branch of the B.M.A. on the subject. Malaria has increased with the opening of the country, as it usually increases under such changing conditions and as it sometimes increases even during the process of bonification. In this connexion, the Chairman reminded members of the Association that, about twenty years ago, Sir Frederick Treves wrote in one of his books (" A Holiday in Uganda ") that there was no malaria in Nairobi. All this is changed now, and Col. James said in his lecture that, to-day, " there is a high incidence of endemic malaria in Kenya as a whole, and the risk to European and other immigrants is serious." He emphasized the view that malaria is a house disease ; in England, malaria affected certain houses which, being damp and uncared for, afforded shelter to mosquitoes, and it affected certain families who were so careless that they neglected their homes, did not object to being bitten by parasites, and took no precautions. He gave an illustration of similar conditions among white settlers in Kenya, where he found a farmer, his family, and all his labour-force, infected with malaria. His house had a thatched roof, wattle-and-daub walls, and a mud floor, and 5 out of 38 anopheles caught in it were carrying sporozoites. As a means of dealing with malaria in the native reserves, Col. James recommended methods of bonification which would improve social conditions by the introduction of agricultural and industrial welfare schemes.

With reference to the prophylactic value of quinine, it had been found negligible in artificially induced malaria in England. He thought that the more satisfactory results obtained in the prophylactic treatment of bird malaria were due to the conveyance of the infection by means of

the inoculation of blood containing schizonts, whereas, in the human experiments, which he had conducted in England, sporozoites (which are tissue parasites) were inoculated by the bites of mosquitoes. He said that nevertheless he did not like it to be thought that he held the opinion that prophylactic quinine was useless. The subject was difficult, and the only sure knowledge was that quinine would not prevent infection, though it might prevent clinical attacks while it was being taken. The infected person who continued quinine regularly was subject to slight rises of temperature and periods of indisposition which represented suppressed attacks, and if he neglected the daily dose he went down with a true clinical attack within 2 or 3 days. A person taking prophylactic quinine was also liable to an attack if he were obliged to undergo hardship or exposure. Although it was not entirely satisfactory, it had to be used in certain cases; for example, for troops in the field who had to be kept fit to carry on their duties during a limited period. Whether it should be used by settlers on farms in Kenya could only be decided for individual cases. "It is not a method," he concluded, "for which a general rule is applicable."

W. F.

GARNHAM (P. C. C.). **Malaria in Kisumu, Kenya Colony.**—*Jl. Trop. Med. & Hyg.* 1929. Aug. 1 & 15. Vol. 32. Nos. 15 & 16. pp. 207–216; 221–231. With 12 text figs. [45 refs.]

Kisumu is a town of over 7,000 inhabitants, 150 of whom are Europeans, situated at the terminus of the Kenya and Uganda Railway, on a small hill nearly 4,000 feet above sea level, overlooking the Victoria Nyanza. There is a constantly high rate of sickness due to malaria, chiefly subtertian; about 200 patients are treated every month, and there are occasional cases of blackwater fever among the European and Indian sections of the inhabitants. This endemic malaria the author attributes to *A. funestus* which is almost always present in such numbers that an increase in its density has no appreciable effect on the malaria curve. Epidemic malaria occurs after the long spring rains, and is attributed to *A. costalis* which appears at that season in great numbers. The spleen rate was found to be an unsatisfactory measure of the amount of malaria in Kisumu; the parasite rate in children between 4 and 10 years old was nearly four times as high as the spleen rate. The species of anopheles found in the district were: *A. gambiae* (*costalis*), *A. funestus*, *A. pharoensis*, *A. mauritianus*, *A. pretoriensis*, *A. squamosus*, *A. maculipalpis* and *A. symesi* Edwards, a new species found by the author. *A. costalis* was found breeding "in everything and everywhere" in crowded parts of the town and in secluded harbours, preferably in stagnant water. *A. funestus* was found to be fastidious in its choice of breeding-places which were limited to streams overgrown with weeds, to drains, and to papyrus-swamps, away from the town; its larvae were as difficult to find as those of *A. costalis* were easy. Twenty-five huts were examined for mosquitoes every week, from March, 1926 to January, 1928. Almost the only anopheles caught were *A. funestus* and *A. costalis*; *A. funestus* was in the majority except after the long rains. Its density did not vary with the rainfall, because it bred in permanent water; its density was greatest in the huts near

to these permanent breeding places. *A. costalis* was present in greatest numbers after the long rains which filled up and multiplied the casual collections of water in which it bred. As these temporary breeding places were to be found everywhere in the neighbourhood of the huts, the density of *A. costalis* was not related to the distance from the swamps and streams. The habits of the adult *funestus* and *costalis* were similar; they did not appear to leave the huts immediately after feeding; more than 300 *funestus* were frequently collected in a single hut in the daytime and much the same number at night. Female anopheles were found to abandon huts which had been vacated by their human occupants, but the number of male mosquitoes was actually increased. The author was unable to catch anopheles sheltering in the trees and bushes near the breeding-grounds. He concludes that the enormous permanent breeding grounds in the neighbourhood of Kisumu render the eradication of malaria impracticable, and he recommends the treatment of cases and carriers, "the deflection or elimination of the domestic anopheline adult, and, lastly, and leastly, anti-larval measures."

W. F.

Durieux (C.) & Sall (M.). Nouvelles recherches sur l'index du paludisme à Dakar durant la saison fraîche. [**A New Inquiry into the Malarial Index at Dakar, during the Cold Season.**]—*Bull. Soc. Path. Exot.* 1929. July 10. Vol. 22. No. 7. pp. 618–622. [4 refs.] [Pasteur Inst., Dakar.]

The authors examined 153 children between 2 and 15 years of age, in a village on the outskirts of Dakar, during January, 1929. Parasites were found in 24 per cent. At a previous examination, made eight years before, the rate of infection was 50 per cent. The improvement is attributed to the anti-mosquito measures undertaken in connexion with the campaign against yellow fever at Dakar.

W. F.

Walravens (P.). La malaria à Elisabethville. Conditions de la lutte contre la maladie. [**Malaria at Elizabethville. The Conditions of the Campaign against the Disease.**]—*Ann. Soc. Belge de Méd. Trop.* 1929. Oct. 30. Vol. 9. No. 3. pp. 197–202. With 1 plan. [Bact. Lab., Elizabethville.]

There are many species of anopheles in the neighbourhood of Elizabethville, but only two, *A. costalis* and *A. funestus*, are commonly found in the town; *A. costalis* predominates, and of 544 anopheles caught in houses, 89 per cent. were *A. costalis* and 11 per cent. *A. funestus*. *A. costalis* breeds almost anywhere, in river pools where the flow is retarded, in the edges of streams, in ditches, and in small collections of muddy water; it generally prefers places which are exposed to the sun. The breeding places of *A. funestus* were not discovered (See Garnham, above.) The reservoirs of infection are the native children, in 90 per cent. of whom parasites were found at a single examination.

W. F.

Boyd (Mark F.) & Aris (F. W.). **A Malaria Survey of the Island of Jamaica, B.W.I.**—*Amer. Jl. Trop. Med.* 1929. Sept. Vol. 9. No. 5. pp. 309–399. With 13 figs., 10 maps, 7 charts & 2 plates. [19 refs.]

Endemic malaria in Jamaica is almost entirely confined to the very fertile coastal plains where agriculture is most successful. The bulk of this fertile land is the property of large estates. The settled population is small; most of the labourers come from the plateau of the interior, and they are very susceptible to malaria. In the coastal region there are several foci where malaria is always intense and does not vary; but in the surrounding country there is not much malaria except when there is a heavy rainfall which provides numerous breeding places. Twenty years ago there was much more malaria than there is to-day; 60 years ago there was as little as there is now, and there appear to be cycles of malarial intensity which accompany cycles of rainfall. *A. albimanus* is regarded by the authors as the important carrier. *A. crucians* and *A. vestitipennis* may act as carriers, but they are too scarce to be important. *A. grabhami*, which also occurs on the island, is exonerated because its distribution is much wider than that of malaria and it is prevalent over the island plateau where there is no fever. W. F.

Federated Malay States. **Annual Report of the Malaria Advisory Board for the Year 1928** [Hoflin (J. W.)].—12 pp. 1929. Kuala Lumpur.

Several interesting questions are dealt with in this report. The malaria of rice fields has been under investigation for several years, and a new sub-committee which was appointed to go into the matter reported that as this was part of the general problem of malaria in the country it was useless to persist in a separate study of the rice fields, and that the malaria of the rice fields in the hilly districts was so largely due to *A. maculatus* that the problem was inseparable from the general one of the malaria of hilly districts.

Reports on larvicidal oils obtained from scrap rubber were considered and the Board came to the conclusion that they were less efficient and more costly than the mineral oil mixtures already in use. Reports from the Institute for Medical Research on the uselessness of aseplene and the value of plasmoquine were considered [see this *Bulletin*, Vol. 26, pp. 380 & 931] and it was agreed that the Government should be approached with a view to preventing the advertising and sale of such drugs as aseplene.

The Board agreed that systematic investigation of the seasonal pathogenicity of anophelines was desirable, in view of the fact that it had been brought to their notice that at times it was difficult to infect *A. maculatus*, the principal local carrier.

In connexion with a proposal to screen the wards of hospitals, the Entomologist described experiments and reported that 25 per cent. of the anophelines used passed through a gauge of 12 meshes to the inch, and 6 per cent. through one of 14 meshes. He recommended that nothing larger than 16 mesh should be used.

The question of damage done to growing rice by oil used as a larvicide was considered. In one district, where oiling was alleged to have injured padi, parasites were discovered in the plants, and it was uncertain whether the damage was due to the oil or to the parasites. The matter is under investigation. (See this *Bulletin*, Vol. 26. p. 909, Damage done to fish by oiling.) W. F.

Federated Malay States. **Annual Report of the Malaria Research Division for the Year 1928** [Green (R.)].—*Federated Malay States Ann. Rep. Med. Dept. for Year 1928.* Appendix V. pp. 75–85.

This report deals principally with quinine, plasmoquin and dimeplasmin in the treatment of malaria. These investigations have formed the subject of Bulletins issued by the Institute for Medical Research at Kuala Lumpur which have been reviewed already in this *Bulletin.* A substance widely advertised, under the name of aseplene, as a cure for malaria, was tried on ten cases, but no evidence was obtained to show that it had any effect on the parasites. There are several other items of interest in the report: (1) The glucose tolerance was investigated in 21 cases of malaria; it was found to be lower than normal in 16 of the cases, but there was no glycosuria in any of them. The urinary diastatic index and the faecal fats were normal in all. (2) *P. falciparum* was cultivated from three cases, but there was no evidence of a second generation arising from merozoites entering corpuscles, though ring-forms developed up to the stage of schizogony. (3) It was found that when 5 grains of quinine hydrochloride were administered in powder form to three healthy men, Mayer's reaction became positive in 40 minutes, and continued so for 10 hours; but when quinine alkaloid, quinine ethyl carbonate, or cinchonine were given, the reaction took three or four times as long to appear and its duration was no longer. (4) In staining blood films, it was found that better results were obtained with Leishman's stain when the distilled water was adjusted to a pH of 7·2 by the addition of 0·1 per cent. potassium carbonate.

W. F.

Terdschanian (A.). Die Malaria in Dagestan. [**Malaria in Daghestan.**]—*Arch. f. Schiffs- u. Trop.-Hyg.* 1929. Nov. Vol. 33. No. 11. pp. 587–592. [4 refs.]

The Republic of Daghestan lies in the eastern part of the Caucasus. Many biting insects are met with everywhere; in the open, 1 Anopheles to 10–15 Culex, and in rooms, 1 Anopheles to 2–3 Culex were observed. The anopheles were *A. maculipennis* Mg., *Hyrcanus* var. *pseudopictus* Grassi, *sacharovi* Fawr. and *algeriensis* Theob. In addition to anopheles, sandflies were specially abundant in Tschir-Yurt, the species being *P. papatasii* Scopoli, and *perniciosus* Newstead. The malarial indices are throughout high. The author considers that the Republic of Daghestan is heavily infected with malaria. The conditions responsible for it are: the flooding by the large rivers in the northern and central portions of the country; the primitive artificial irrigation in the south, which, when the air temperature is suitable, leads to the development of huge numbers of Anopheles; and also the ignorance and poverty of the population, with the complete absence of prophylactic measures.

E. D. W. Greig.

Marchoux (E.). Prophylaxie du paludisme. Le paludisme dans les Dombes et en Camargue. [**The Prevention of Malaria. Malaria in the Dombes and in Camargue.**]—*Rev. d'Hyg. et de Méd. Préventive.* 1929. Oct. Vol. 51. No. 10. pp. 721–744. With 2 maps. [1 ref.]

The region of the Dombes is a hilly plateau with basin-like valleys between the hills; for the last 700 years it has been the custom to dam

these valleys and convert them into fishponds or *étangs*. In olden days, 90 per cent. of these *étangs* belonged either to the clergy or to the nobles; the rest of the country was barren and the inhabitants lived in dire want. Several municipalities reported, in 1790, that the condition of the people was most wretched; they stated that the deaths exceeded the births in number, and they attributed the unhealthiness of the district to the malign influence of the *étangs*. The ravages of malaria were particularly severe in the early part of the nineteenth century, and, in 1857 two-thirds of the population were affected. Between 1863 and 1870 the total area of the *étangs* was reduced from 14,000 to 8,000 hectares and, by their drainage, large tracts of most fertile land were made available for agriculture. Subsequently the social condition and the health of the people improved enormously, and, between 1880 and 1890, malaria came to an end. In 1901 legal sanction was sought and obtained to construct new *étangs*, and they were extended until they covered almost as much ground as they had occupied in the days when malaria was prevalent; but the disease did not return. The *étangs* which used to bring disease now bring wealth and health, for they are a source of great revenue. They are used as fish ponds for two years; at the end of each year the water is run off and the fish are sold at a large profit. In the third year they are drained and cultivated, and they yield huge crops. The people are now well-to-do, they have many cattle (which are the normal hosts of the anopheles), plenty of agricultural machinery, and they live in comfort. In spite of the old, ill-lighted houses, in spite of an abundance of anopheles (*A. maculipennis*), and in spite of some malaria carriers, there is no spread of the disease. This is attributed by Professor Marchoux to the improvement in the lot of the people which has followed the improvement in agriculture, to their increased resistance due to better food, and also to the greater care which they take of themselves.

In the Camargue, near the mouth of the Rhone, there are also *étangs*. There are not so many anopheles in this district as in the Dombes, yet here benign tertian malaria is prevalent. The district consists of large estates, many of which belong to absentee landlords; the farm workers are imported foreign labourers employed by contractors. These labourers live under bad conditions, they sleep in cow-sheds and stables, or wherever they can find shelter; moreover, they are ignorant and suspicious, and they take no care of their health. Professor Marchoux believes that better methods of agriculture and an extension of cultivation would improve social conditions and banish malaria from the Camargue as they have already banished it from the Dombes. [See also this *Bulletin*, Vol. 24, pp. 345–8.]

W. F.

Pecori (G.) & Escalar (G.). Relazione sulla campagna antimalarica dell'anno 1928. (**Report on Malarial Prophylaxis Campaign of 1928.**) —*Riv. di Malariologia*. 1929. Sept.–Oct. Vol. 8. No. 5. pp. 481–533. With 3 figs. [English summary p. 633.]

During 1928, endemic malaria in Rome and its environments was a little less severe than in the previous year. In all there were 2,373 cases, 62 less than in 1927. Malignant tertian accounted for 1,057 of these, 423 being primary attacks, 631 relapse cases. Of benign tertian there were 1,284; 493 primary, 791 relapse; of quartan there were only 32, 19 being primary. The population is stated to be about 70,000, which

would give a morbidity rate of 3·39 per cent. The peak of primary benign tertian was in July and August, with 110 and 119 cases respectively; most relapse cases (163) occurred in July. As regards primary malignant tertian the peak occurred in August (134 cases), while relapses (117) were most numerous in September.

Antilarval measures were undertaken in 20 districts. In Ostia Antica, between January 1st and December 31st, 32,807 mosquitoes were captured, 914 of them males; 30,699 were caught in the stables and pigsties, 2,108 in the houses.

H. Harold Scott.

Falleroni (Domenico). Discussione sulla zooprofilassi. Norme per le costruzioni rurali in zone malariche. Nota sesta. (**Discussion on Zooprophylaxis. Principles for constructing Rural Buildings in Malarial Regions.**)—*Riv. di Malariologia.* 1929. Sept.–Oct. Vol. 8. No. 5. pp. 590–606. With 6 text figs. [4 refs.] [English summary p. 634.]

This article does not lend itself to abstraction. It is one for veterinary architects to ponder over. The author shows that the interposition of stables and piggeries between the source of the mosquitoes and an inhabited dwelling affords a very effective screen provided there is no direct line from the stables to the house and that the distance between them is at least 10 metres. Various plans are depicted to show the principles of construction of such "animal houses" to utilize the attraction of the latter and intercept the mosquitoes before they invade the human dwelling.

H. Harold Scott.

Swellengrebel (N. H.). La dissociation des fonctions sexuelles et nutritives (dissociation gono-trophique) d'*Anopheles maculipennis* comme cause du paludisme dans les Pays-Bas et ses rapports avec "l'infection domiciliaire." [**The Dissociation of the Sexual and Nutritive Functions—"Gono-trophic Dissociation"—in** *A. maculipennis* **as the Cause of Malaria in the Low Countries, and its Connexion with "House Infection."**]—*Ann. Inst. Pasteur.* 1929. Oct. Vol. 43. No. 10. pp. 1370–1389. With 4 text figs. [28 refs.] [Inst. of Trop. Hyg., Amsterdam.]

The theory of "house infection" represents the house as the principal centre of infection, and the practical methods of prevention which it teaches are the destruction of all the mosquitoes which can be found within the houses and the construction of houses unsuitable for their concealment. Many authorities deny the truth of this theory and affirm that the mosquitoes leave the houses when they have fed, or at any rate long before they become infective. The author believes that a study of malaria in the Low Countries shows that, under certain conditions, there is a force which keeps the mosquitoes "fixed" in houses over long periods. In the malarious parts of the Low Countries there is only one anopheles in a house for every 200 in cow-sheds. An anopheles which becomes infected in a house during the summer must leave it, at the latest within a few days, in order to lay its eggs; that is to say long before it becomes infective, and the chances that it will find its way back to a house again are less than 1 in 200. It is not surprising therefore that a search for infected mosquitoes, made in the summer,

was unsuccessful except for a few in the earliest stages of öocyst formation, and it appears strange that malaria can exist under such conditions.

The author's explanation is as follows:—A great change takes place in the habits of the mosquitoes when the autumn comes; egg-laying ceases, and as they no longer wish to leave the houses "fixation" occurs. Though they have stopped laying they do not stop feeding, but continue to bite for several months. The "fixation" increases the numbers of mosquitoes within the houses, because, though they continue to enter, there is nothing to induce them to go out again. The female mosquitoes in the houses do not attain their greatest number until October, when the males have disappeared and there are no larvae left in the breeding-places. During fixation, the parasites within infected mosquitoes become sporozoites and these are inoculated into fresh hosts when the mosquito feeds. In spite of this, hardly a case of malaria occurs in the autumn; notwithstanding their infection, the bites of the mosquitoes appear to be sterile. But this is not really the case, for the malaria declares itself in the spring after an incubation of six to nine months. (See JAMES, NICOL, and SHUTE above, p. 183.) This explains why the yearly outbreak of benign tertian malaria in the Low Countries reaches its height at the period of minimum anopheline density which occurs in April, about four months before the maximal frequency of infected anophelines.

The author considers that the continuation of blood-sucking by mosquitoes when they have ceased laying is a most important factor in the epidemiology of malaria. This he calls "Gono-trophic Dissociation." Malaria in the Low Countries is limited to certain districts; other districts where breeding-places are as numerous remain free, although there are four to six times as many anopheles "fixed" in the houses in the autumn. This freedom is ascribed to "Gono-trophic Concordance"; that is to say, the mosquitoes in these non-malarious places cease to suck blood when they cease to lay eggs. In places where the mosquitoes show gono-trophic concordance, there is no malaria even if the anopheline density is very high. The author does not minimize the importance of cow-sheds; without them, the infected mosquitoes which leave houses to lay their eggs would return again to houses for food and would infect the inmates. Cow-sheds, nevertheless, are powerless to prevent the autumnal transmission, which is absent only under the conditions of gono-trophic concordance.

The anopheles with gono-trophic dissociation show certain morphological differences from those with gono-trophic concordance; the average length of their wings is less and the average number of their maxilliary teeth is greater. Moreover, only 2 to 10 per cent. of them show hypertrophy of the fatty bodies, while 70 to 90 per cent. of the group with gono-trophic concordance have this hypertrophy.

The author thinks that gono-trophic dissociation, or some analogous condition, may play an important part in countries beyond the temperate zones, and suggests that it may influence the seasonal incidence of malaria.

W. F.

MURPHY (R. A.) **Microscopic Diagnosis of Malaria on a Group of Tea Estates.**—*Indian Med. Gaz.* 1929. Oct. Vol. 64. No. 10. pp. 557–558.

Dr. Murphy is in charge of a group of tea estates in South Sylhet, Assam, in most of which the spleen rate is about 80 per cent.; 61 per

cent. of the malaria is due to *P. falciparum.* The effects of this high rate of infection are much less severe than would be expected ; in the last seven years there has been no case of blackwater among the members of the European staff, and the general death rate among the coolies is only 12 to 15 per cent. " The coolies are for the most part old settlers, well acclimatized, and must possess considerable immunity." The author finds that a short course of quinine is " ineffective and does not bear out the results of experiments in a temperate climate." In order to test the accuracy of the malaria returns sent in by the sub-assistant surgeons from the tea gardens, instructions were issued to them that blood-films should be taken from all patients showing a rise of temperature, whatever their complaint. The results of the examinations of the films were then compared with the diagnoses. " The figures from one estate, with a sub-assistant surgeon rather above the average, show how fallacious returns are " :—

Diagnosed malaria, and parasites found	380
Diagnosed malaria, and no parasites found	200
Diagnosed as other diseases, and parasites found	107
Diagnosed as other diseases, and no parasites found ...	110

The method recommended by SINTON was employed in the preparation of the films. A thick film at one end of the slide was divided from a thin film at the other end by a grease-pencil line, and after the addition of water to the Romanowsky stain on the thin film, the mixture was drawn over on to the thick film.

W. F.

BARBER (M. A.) & KOMP (W. H. W.). **Method of preparing and examining Thick Films for the Diagnosis of Malaria.**—*Public Health Rep.* 1929. Sept. 27. Vol. 44. No. 39. pp. 2330–2341. With 5 text figs. [1 ref.]

The authors insist on the importance of a good quality Giemsa strain, and that the water used for diluting it should be neutral or slightly alkaline and free from salts. They employ Grübler's Azur Eosin solution, which can be obtained from Karl Hollborn of Leipzig. The distilled water should have a reaction of pH 7·0 to 7·2. The blood can be conveniently collected from a puncture made on the dorsum of the middle finger a little below the base of the nail, care being taken not to touch the patient's skin with the slide, which must be free from grease. A drop of blood, about three or four times as much as is required for a thin film, is taken onto the slide near one end, and is spread out with the pricking needle over an area the size of the little finger nail. The patient's number is written on the other end with a grease pencil. The slide is placed, film side downwards, in its groove in the slide-box, which is stood on its end until the blood is dry enough not to run. Slides kept over-night in a closed box are sufficiently dry for staining next morning. Alternatively, the box may be left without its lid in the incubator for 60 to 75 minutes. If drying is insufficient, the film will come off in the staining bath ; if it is too prolonged, the parasites will not stain properly. If it is necessary to keep the slides for some time before they can be stained, excessive drying can be prevented by wrapping them in paraffined (not kerosined) paper. The authors find that preliminary dehaemoglobinization and fixation of thick films are unnecessary. Sufficient stain for 25 slides is prepared by putting 60 or 70 drops (1·3 cc.) of Giemsa solution in the staining dish and adding 75 cc. of water. The slides are left in the stain for about half an hour. Differentiation is obtained by placing them in distilled water for five minutes. If the background is deep blue and the leucocytes almost black, the preparation is overstained,

Thin films may be made on the same slide as the thick films, at the other end, and the labelling done with an ordinary lead pencil on the thin film. The thin film can be stained later with Leishman's stain, if it is necessary to determine the type of parasite; a line drawn across the slide with a grease pencil prevents the stain running on to the thick film. It is unsafe to call anything a parasite unless it shows a red dot of chromatin associated with a blue mass of cytoplasm. Stained films can be preserved by covering them with liquid paraffin, or vaseline, and storing away from light. Immersion-oil must first be removed with xylol, after warming the slide slightly, and the xylol removed with absolute alcohol. When large numbers of slides require staining, small pieces of cardboard can be placed between the numbered ends, and the slides held in place by a rubber band. The block of slides can then be placed upright in the staining dish, with sufficient staining solution to cover the thick films at the other end.

W. F.

BARBER (M. A.) & KOMP (W. H. W.). **The Seasonal and Regional Incidence of Types of Malaria Parasites.**—*Public Health Rep.* 1929. Aug. 23. Vol. 44. No. 34. pp. 2048–2057. [1 ref.]

The authors examined 1,517 cases of malaria, most of which came from the Mississippi Delta. Only 41 per cent. of the infections in white persons were due to *P. falciparum*, but in coloured people 66 per cent. were due to this form of parasite. Benign tertian infections predominated among the whites in the spring, and subtertian in the autumn; in coloured people such seasonal variation was very slight. The authors attribute the different incidence of malaria in the two races to the lesser resistance of *P. falciparum* to the action of quinine, which is taken by the whites but is seldom taken by the coloured people. Crescents were found in 41 per cent. of the subtertian cases.

W. F.

BARBER (M. A.) & KOMP (W. H. W.). **The Malaria-Parasite Index of School Children in Leflore County, Miss.**—*Public Health Rep.* 1929. Sept. 6. Vol. 44. No. 36. pp. 2156–2162. [1 ref.]

Leflore County is situated in the alluvial plain forming the delta between the Mississippi and Yazoo rivers. The authors examined the children in a number of schools at different seasons during a number of years. During the years 1925 to 1929, 3,697 children were examined and malaria parasites were found in 9·5 per cent. The white children in both town and country, and the coloured children in the towns, showed approximately the same rate of infection, namely, 4·0 per cent.; but the coloured children in the country districts gave a rate nearly four times as high, namely, 15·6 per cent. In some schools there were wide variations in the parasite rate from year to year. The number of parasite cases among negro children was approximately double that detected at a single examination. The great majority of the negro children appeared to be in normal health in spite of their parasites; they received little treatment, and doubtless the majority "just wore their chills out." Many examples of "family malaria" were encountered in which certain families suffered more than their neighbours, not because they were exposed to more anopheles, but because they received less treatment or were less resistant.

W. F.

KLOTZ (Oskar). **Necrosis of the Liver in Malaria.**—*Amer. Jl. Trop. Med.* 1929. July. Vol. 9. No. 4. pp. 241–248. [9 refs.] [Dept. of Path., Univ., Toronto.]

The author, who is a member of the Yellow Fever Commission of the Rockefeller Foundation, has studied the morbid anatomy of the liver in malaria and blackwater fever with special reference to the differential diagnosis from yellow fever, and he has found that there is no difficulty in distinguishing them. In acute malignant malaria, a necrosis preceded by fatty degeneration begins in the central zone and spreads outwards towards the periphery of the lobule ; malarial pigment is to be seen in the Kupffer cells, and parasites are present. In yellow fever, on the other hand, the necrosis begins in the middle zone of the lobule, and, though it spreads towards the centre, it leaves a ring of living cells around the central vein. The fatty changes are more intense in yellow fever. Councilman's hyaline acidophile bodies are to be found within the cytoplasm of the cells, and the nuclei undergo degenerative changes like those seen within the nuclei of the nerve-cells in herpes, which are said to indicate the presence of a virus. The necroses which the author found in the liver of a case of blackwater fever were similar to those found in malaria, and he concludes that " the liver necroses in blackwater fever are dependent upon the effect of the malarial infection alone."

W. F.

MICHELETTI (Ettore). Contributo allo studio delle localizzazioni parassitarie nelle infezioni malariche perniciose. (I. Nota preliminare sulle localizzazioni miocradiche). [**Localization of Parasites in Subtertian Malaria. (I. Localization in the Myocardium).**] —*Ann. di Med. Nav. e Colon.* 1929. Sept.–Oct. Year 35. Vol. 2. No. 3/4. pp. 162–180. With 6 figs. on 3 plates. [15 refs.]. [Inst. of Path. Anat., Univ., Rome.]

The author describes the histological changes in two patients dying from subtertian malaria. The main alterations noted are a myocarditis with fragmentation and necrosis of the fibres, and the presence of parasites in the veins, but no engulfing of them or of pigment by the endothelial cells of the capillaries, thus differing from the changes seen in the organs, liver, spleen, bone-marrow, etc.

H. Harold Scott.

KING (W. V.). **On the Development of Malaria Parasites in the Mosquito.** —*Amer. Jl. Hyg.* 1929. Nov. Vol. 10. No. 3. pp. 560–564. With 21 figs. on 7 plates. [1 ref.]

This paper is illustrated by a very beautiful series of photographs showing the sexual cycle of malaria parasites within the mosquito. Some of the mosquitoes' stomachs shown in the photographs contained enormous numbers of öocysts ; one was so covered with them that the photograph has a mulberry-like appearance and the actual number of cysts was estimated at 600. Such numbers are rare ; in the majority of the mosquitoes examined by the authors there were less than 10

öocysts to be found. No evidence was obtained that the infection was hurtful to the mosquitoes ; the average life following an infective blood meal was 16·5 days for 83 mosquitoes which became infected, and 15·2 days for 62 which remained uninfected. The author recapitulates the development of the parasites in the mosquito as follows : The macrogametocyte is fertilized in the insect's stomach and becomes an active zygote which penetrates the stomach wall and comes to rest between the epithelial cells and the elastic muscular coat ; there it acquires a cyst wall and becomes an öocyst, about 7 μ in diameter, with hyaline protoplasm and a clump of dancing malaria pigment. The öocyst increases greatly in size, and bulges out into the body cavity of its host, remaining attached to the muscular wall by a very restricted neck of muscular tissue. When it has reached a size of 35 to 45 μ, the nucleus and protoplasm divide into sporoblasts ; these become separate centres for the formation of sporozoites which appear as granular streaks. As the sporozoites grow, the number of sporoblasts is reduced by coalescence until the sporozoites assume a radial arrangement. At length the öocyst is filled by a squirming mass of sporozoites which rupture it and make their way through the body fluid to the salivary glands, where they infect either the central or the paired side lobes. The time required for development in the mosquito is usually given as 10 days. The shortest times observed in the author's experiments were 12 days with *P. falciparum*, at a mean temperature of 70° F., and 14 days with *P. vivax* at 74° F.

W. F.

King (W. V.). **Additional Notes on the Infection of Anopheles with Malaria Parasites.**—*Amer. Jl. Hyg.* 1929. Nov. Vol. 10. No. 3. pp. 565–579. With 1 text fig. [3 refs.]

The author gives an account of the dissection of a number of anopheles, some of which had been fed on gametocyte carriers while others had been caught in native houses. The species were *A. quadrimaculatus*, *A. punctipennis*, and *A. crucians*. Mosquitoes fed on carriers became infected to the extent of 52·2 per cent., with a range varying between 11·1 and 94·4 per cent. in different batches. Infections were obtained from 10 out of 12 benign tertian patients, and 5 out of 6 subtertian patients. No significant differences were found as regards the percentage of successful infections, either between the different species of anopheles or between the different species of malaria parasites. Little or no correlation was found between the number of gametocytes in the blood and the proportion of mosquitoes which became infected, or the number of öocysts which were produced. In some of the mosquitoes, degeneration of the öocysts occurred when they were almost full grown ; the cause of this was not discovered, nor is it known if such degeneration occurs under natural conditions. During the investigation of natural infections there were several instances in which infected mosquitoes were taken in consecutive collections from the same house over periods of days or weeks ; in one such house, 17 out of 50 mosquitoes were found to be infected. The author kept his mosquitoes singly, in glass tubes, at a temperature of 45° to 55° F., until they were required for experiment.

W. F.

CHEVALLIER (Paul) & SCHWOB (R.). Transmission fortuite du paludisme inoculé dans un service hospitalier. [**The Accidental Transmission of an Inoculation Strain of Malaria in a Hospital.**]—*Bull. et Mém. Soc. Méd. Hôpit. de Paris.* 1929. Oct. 28. Year 45. 3rd Ser. No. 27. pp. 1189–1191. With 1 chart in text.

The authors report the occurrence of a case of accidental malaria in a Paris hospital where a large number of paralytics were undergoing treatment by the Wagner-Jauregg method. The patient in question, who had never been exposed to malaria, had been undergoing treatment with a new drug administered by inoculation, when nine days after its commencement she developed an attack of malaria with parasites in the blood and was cured by quinine. There were many mosquitoes in the hospital, but no anopheles could be found amongst them. The authors suggest that this accidental infection was conveyed direct on the proboscis of a culicine immediately after it had feed on a paralytic under treatment or that the carrier was an anopheles which had strayed in from the suburbs of the city. M. BRUMPT suggests that the infection was conveyed by the syringe employed in the inoculation of the new drug. [Though the authors do not agree with him, this certainly seems a more reasonable explanation.]

W. F.

CHEVALLIER (Paul). Quelques particularités des réimpaludations thérapeutiques. [**Some Peculiarities of Re-infections with Therapeutic Malaria.**]—*Bull. et Mém. Soc. Méd. Hôpit. de Paris.* 1929. Oct. 28. Year 45. 3rd Ser. No. 27. pp. 1192–1194. With 3 charts in text.

It is not always difficult to re-infect people who have had malaria. Sometimes the incubation is much shorter and the fever higher than in those who have never suffered from the disease before. The author thinks that parasites are already present in the blood of such cases, though their numbers are insufficient to give rise to fever, and that the inoculation of infected blood increases them to the point necessary to cause an attack.

W. F.

BIGGAM (A. G.). **Malignant Malaria associated with the Administration of Heroin intravenously.**—*Trans. Roy. Soc. Trop. Med. & Hyg.* 1929. Aug. 26. Vol. 23. No. 2. pp. 147–153. With 1 plate.

During the last few years patients have been admitted occasionally to the Kasr el Aini Hospital, showing signs of repeated puncture of the veins of the arms, due to the intravenous administration of heroin. A photograph is given, showing the extensive pigmentation and scarring of the superficial veins of the arms which are characteristic of the drug addict. During the last few months a much larger number of these cases has been admitted. Intravenous injections have been popularized in Cairo by the tartar emetic treatment of bilharzial conditions, and the author thinks that it is for this reason that the heroin is given intravenously. It is injected with an unsterilized syringe; a little blood is sucked up before giving the inoculation to make sure that the needle is in the vein, and again at the end of the operation to ensure that the last drops of the drug are washed out of the syringe and injected into the addict.

During April 1929 certain of these heroin addicts were admitted with irregular temperatures, and their blood was found to contain malignant tertian parasites. This type of malaria is practically unknown in Cairo; no cases had been admitted to the hospital—apart from the drug addicts—for at least two months, and the author concludes that the infection was communicated during the injection of the heroin. Details of ten cases are given; they all had crescents in their blood, and Major Biggam considers that, unless steps can be taken to prevent the inoculation of heroin in this manner, there is grave danger that the disease may be conveyed to the general population of the city by the agency of mosquitoes. The Editor of the *Transactions* quotes other instances of the accidental conveyance of malarial infection by the syringe in giving salvarsan injections and in the transfusion of blood.

W. F.

Green (Richard). **The Relationship of the Blood Groups to Immunity from Malaria and to Gametocyte Formation.**—*Trans. Roy. Soc. Trop. Med. & Hyg.* 1929. Aug. 26. Vol. 23. No. 2. pp. 161–166. With 4 text figs. [2 refs.] [Inst. for Med. Research, Kuala Lumpur, F.M.S.]

The distribution of the four blood groups was investigated among 1,000 Tamils with malaria and 1,000 who were free from it. No connexion was traced between the incidence of the four blood groups, immunity to malaria in general, immunity to species of parasite, or the development of gametocytes. The distribution of the blood groups was as follows: Group (1) 145. Group (2) 391. Group (3) 671. Group (4) 793.

W. F.

Ciuca (M.), Ballif (L.), Vieru (M.) & Stirbu (A.). Contrôle de l'immunité dans le paludisme par transfusion de sang virulent. [**The Transfusion of Virulent Blood as a Test of Immunity in Paludism.**]—*C.R. Soc. Biol.* 1929. Oct. 18. Vol. 102. No. 26. pp. 189–191. [1 ref.]

The authors found that persons who have become immune to the subcutaneous inoculation of benign tertian malaria, either as the result of therapeutic injections or long residence in an endemic area, are also immune to the transfusion of 65 to 220 cc. of citrated blood containing parasites. They recommend the transfusion of virulent blood as the best method of transmitting experimental infection.

W. F.

Rosenberg (Max). Die Malaria in ihren Beziehungen zu Gonorrhöe, Lues und Neurolues. [**Malaria in Relation to Gonorrhoea and Neuro-Syphilis.**]—*Arch. f. Schiffs- u. Trop.-Hyg.* 1929. Sept. Vol. 33. No. 9. pp. 463–467.

As regards gonorrhoea, the author divides the cases into two groups: group A includes cases which had suffered from malaria before being attacked by gonorrhoea; group B cases which had not suffered from malaria. The treatment of the gonorrhoea in both groups was on the usual lines, but recovery in group A was much more rapid than in group B.

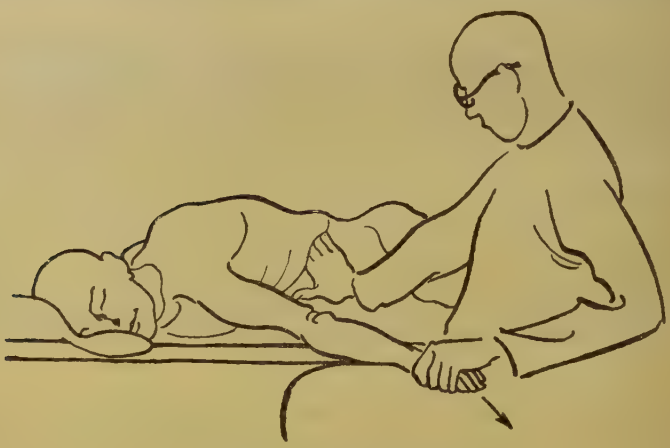
As regards syphilis, he asks two questions : (1) Why do cases of neuro-syphilis occur in towns? (2) Why is it absent in villages? Discussing the relationship of malaria to syphilis, he states that 70 per cent. of the population of villages are infected with malaria, whilst those in towns are protected by the antimalarial measures. He considers that malaria acts both as a prophylactic by preventing the entrance of the spirochaete into the nervous system and by direct cure of the neuro-syphilis.

The observations were made on his Arab patients in Palestine.

E. D. W. Greig.

SCHOTTER (Hans). Zur Methodik der Milzpalpation. [**Spleen Palpation.**]—*Muench. Med. Woch.* 1929. Sept. 13. Vol. 76. No. 37. pp. 1562–1563. With 3 text figs. [Clinic for Infect. Diseases, 2nd State Univ., Moscow.]

The author has employed his method of palpating the spleen for 15 years with good results. He thus describes his procedure. The physician sits on the right of the patient at the level of the pelvis ;



Method of spleen palpation.
[Reproduced from *Muenchener Medizinische Wochenschrift.*]

the patient lies on his back with his head on a pillow. The physician grasps with his left hand the left wrist of the patient and draws the patient on to the right side, and at the same time places his right hand on the pelvis, and pushes it slightly backwards, when a fold develops at the left costal margin. The right hand of the physician is now placed on the abdomen of the patient in such a manner that the tips of the index and middle fingers touch the costal margin in the splenic region, the hand is pressed in with light pressure, but the finger tips are not pushed under the costal margin. The palpating hand is never raised, and tension on left wrist is maintained during the whole examination. This method differs from the ordinary method, where the hand is

pressed towards the spleen, as, by pulling over the left arm of the patient, the region of the spleen is pushed towards the palpating right hand. Deep inspiration naturally makes the palpation easier, and the border of the spleen can be definitely felt and its form and consistence determined. The procedure is made clear by three text figures.

E. D. W. Greig.

Iyengar (M. O. T.) & Sur (Panchanan). **Seasonal Variations of the Spleen-Rate.**—*Indian Jl. Med. Res.* 1929. July. Vol. 17. No. 1. pp. 11–32. With 6 charts. [6 refs.]

The authors conclude, as the result of a study extending over several years in villages of both high and low malarial endemicity, that the spleen rate varies with the seasons. They found that in areas of moderate endemicity it was usually far lower in the dry season than in the wet season. A small rise, which they attribute to relapses due to sudden changes of temperature, often occurred in the early spring. In areas of extreme hyperendemicity the spleens became smaller in the dry season, but as they were still palpable this reduction in size was not sufficient to reduce the spleen index. The authors point out that their observations show the fallacy of judging the relative endemicity of a number of districts by a comparison of spleen rates collected at different seasons. They hope by further observations to obtain a formula by which the average spleen index of the year may be calculated from a single observation made during any particular month.

W. F.

Surbek (K. E.). Ueber die Frequenz der Milzvergrösserung bei den verschiedenen Formen der Malaria. [**Frequency of Splenic Enlargement in Malaria.**]—*Arch. f. Schiffs- u. Trop.-Hyg.* 1929. Sept. Vol. 33. No. 9. pp. 461–463.

Observations were made on cases in hospital, mostly on Javanese land workers. The results are set out in the following statement :—

1. Benign Tertian. (Over 100 blood positive cases.)
   Spleen palpable in 64 per cent.
   Spleen not palpable in 36 per cent.
2. Malignant Tertian. (Over 70 blood positive cases.)
   Spleen palpable in 30 per cent.
   Spleen not palpable in 70 per cent.
3. Quartan. (Only 6 cases.)
   Spleen palpable in all.

The author notes that the numbers are too small to draw definite conclusions. However, it is noteworthy that in 70 per cent. of the malignant tertian cases the spleen is not palpable, and yet the cases were very severe (3 fatal), with a heavy infection of the blood with rings and crescents. In benign tertian the correlation between the parasite index and spleen index is much closer than in the malignant form. The importance of a parasite index in malarial regions in which *P. falciparum* infection occurs is emphasized.

E. D. W. Greig.

Cawadas (Eust.). Les manifestations laryngologiques du paludisme latent. [**The Laryngeal Manifestations of Latent Malaria.**]—*Grèce Méd.* 1929. Mar.–Apr. Vol. 31. No. 3–4. pp. 9–11.

The author, who is a specialist in laryngology at Athens, describes four cases which were sent to him with laryngeal symptoms and slight fever. He found that the upper air passages were congested, but there were no signs of acute or of long continued chronic inflammation. None of the patients gave a history of malaria, but on examination of their blood benign tertian parasites were found and they were quickly and permanently cured by quinine. The author attributes the symptoms, such as hoarseness, cough, and occasional pain on swallowing, to congestion following the action of the malaria parasites on the blood-vessels.

W. F.

Monteleone (Remo). Significato delle modificazioni della frequenza della pulsazioni nella malaria. Studio clinico-sperimentale. (**Tachysphygmia in Malaria.**)—*Riv. di Malariologia.* 1929. July–Aug. Vol. 8. No. 4. pp. 401–435. With 10 graphs. [11 refs.] [English summary p. 479.]

Characteristic variations have been observed in sphygmograms, taken during the course of malarial infections, which sometimes lead to the detection of "masked malarial attacks." Charts of typical benign tertian malaria are given which show that, after the fever has been suppressed by treatment, there may be a rise of pulse rate on alternate days. The author interprets these rises as indications of latent malaria.

W. F.

Matsushima (Rihei), Taguchi (Seihei), Suenaga (Daishiro) & Ohya (Otoichi). **A Case of Raynaud's Disease caused by Malaria.**—*Taiwan Igakkai Shi* (*Jl. Taiwan Med. Soc.*). 1928. Feb. No. 287. [Summarized in *Japan Med. World.* 1929. June 15. Vol. 9. No. 6. pp. 193–194.]

"The authors reported a case of Raynaud's disease, caused by tertian malaria. Since Mulsau reported that Raynaud's disease may be caused by malaria, several cases have been reported, but their case was the first one in Japan. The patient was a soldier, age 25, who entered the hospital with attacks of malaria. The diagnosis was confirmed by blood examination. While in the hospital the patient had remitting attacks of high fever, rapid pulse, and light cyanosis of fingers and tired feeling in the lower extremities. Later, the heart-beat became impure, and the cyanosis increased with typical pains."

W. F.

Ferrão (Pires). De um caso anomalo de urticaria palustre. [**Malarial Urticaria.**]—*Arch. Brasileiros de Med.* 1929. Aug. Vol. 19. No. 8. pp. 435–442.

The patient with *P. vivax* in her blood had attacks of generalized urticaria lasting for 8 hours, on four occasions, the rash disappearing on alternate days. Treatment by methylene blue, 50 cgm. in five capsules, and quinoform, 60 cgm. in a single dose, four hours before the expected attack brought about a cure.

H. Harold Scott.

Smith (S.). **The Malaria Treatment Centre—Kasauli.**—*Jl. Roy. Army Med. Corps.* 1929. Aug. & Sept. Vol. 53. Nos. 2 & 3. pp. 81–93; 173–185. With 2 charts & 1 fig. [1 ref.]

The Malaria Treatment Centre at Kasauli, near Simla, is situated at an altitude of 6,100 feet, and there is no possibility of re-infection. It was inaugurated in 1924, "in the hope of finding a really satisfactory treatment for chronic relapsing malaria." The convalescents live in barracks, where accommodation is available for 150 men. A physical training staff is provided, and all station guards, fatigues, and the like duties are performed by the patients themselves. Thirty beds are reserved at the British Military Hospital for those who relapse. During the year reviewed by Major Smith, 240 convalescents joined the Centre, 84 of whom relapsed and were admitted to hospital while they were there: 77 with benign tertian, 5 with subtertian, and 2 with mixed tertian. It is noted that herpes labialis was present in 26 per cent. of these cases. Most of the men put on 4 or 5 pounds in weight while they were at Kasauli, and added about 10 per cent. to their haemoglobin. Half a pound of cooked liver was given to all those whose haemoglobin fell below 70 per cent., but the author states that it had "no striking curative action." Details of several instructive cases are given. A patient with benign tertian malaria, who continued to run an irregular temperature in spite of quinine, was sent, as a case of resistant malaria, to the hospital, where *Bact. typhosum* was isolated from his stools. Another case illustrates "the fallacy of the argument, brought forward by some, that plasmoquin, in order to produce a cure, must be pushed sufficiently to produce toxic symptoms." The patient, prior to his admission to the Centre, was given a very large toxic dose of plasmoquin owing to a misunderstanding, and he was dangerously ill in consequence; yet he relapsed four times after arrival at the Centre, and was finally invalided home. A series of 16 cases was given a continuous course consisting of 0·06 gram of plasmoquin and 20 grains of quinine daily; 10 of the patients showed toxic symptoms, and treatment had to be stopped after nine or ten days. The most satisfactory results were obtained with plasmoquin 0·04 gram and quinine 20 grains daily. Six patients were given intramuscular injections of 0·03 gram plasmoquin with good results and without pain. The author considers that "expert *daily* supervision is essential in the case of patients undergoing treatment with any form of plasmoquin."

Parosan, "a drug allied to stovarsol," and quinine parosan oxide were administered to a small series of patients. No toxic effects were observed, but malaria parasites persisted in the blood of several of the patients.

W. F.

Segal (M.) & Bloch (J.). Beitrag zur Plasmochintherapie. [**Plasmochin Therapy.**]—*Arch. f. Schiffs- u. Trop.-Hyg.* 1929. Oct. Vol. 33. No. 10. pp. 532–535.

Only 24 cases of malaria were treated. Four were clinically diagnosed, the remainder microscopically, 7 being *P. vivax* infections, 12 *P. falciparum* infections, and 1 quartan malaria. With one exception they were all treated as outdoor cases, and therefore there were certain gaps in the investigation. As the quantity of plasmochin available was limited, only small doses could be given, and varied from 0·01 to 0·04 gm. daily. Cyanosis and pains in stomach were noted in

one case. The authors conclude : (1) Plasmochin, even in small doses, has an extremely powerful gameticidal action. (2) Plasmochin has a much more powerful action on the gametes of *P. falciparum* than quinine. (3) The results of the ambulatory plasmochin treatment must be controlled by many observations at the bedside. (4) Without doubt plasmochin represents a great advance in malaria therapy. In Turkistan, where the investigations were carried out, it was of particular value for the quinine-resistant cases met with there.

E. D. W. Greig.

Torrioli (M.). Sull' impiego della plasmochina nei casi di emoglobinuria da chinina. [**Plasmochin for Patients who have previously exhibited Quinine Haemoglobinuria.**]—*Policlinico.* Sez. Prat. 1929. Sept. 16. Vol. 36. No. 37. pp. 1311–1314. [4 refs.] [R. Inst. Clin. Med., Univ., Rome.]

The question whether to give quinine to a malarious patient in whom, on a previous occasion, its use has been followed by haemoglobinuria is always an anxious one for the tropical practitioner. The author consequently compared after the method of Ghiron (this *Bulletin*, Vol. 24, p. 657), the effects of quinine and plasmochin, thus : In a series of ten tubes were placed 20 drops of plasmochin in graded strengths from 1·0 to 0·1 per cent. To each were then added two drops of a suspension of washed corpuscles of a malarious patient and after 5 minutes at 37° C. two drops of the serum of a haemoglobinuric patient. A similar series was put up using quinine in place of plasmochin. He found that haemolysis occurred much earlier and in much lower concentration with quinine than with plasmochin, and concludes that the latter can be given with safety although a history of previous quinine haemoglobinuria is obtained.

H. Harold Scott.

Hasselmann (C. M.) & Hasselmann-Kahlert (Margarete). Erfahrungen und Zwischenfälle bei der Plasmochinbehandlung autochthoner Malaria in den Tropen. [**Plasmochin Treatment of Malaria in the Tropics.**]—*Deut. Med. Woch.* 1929. Sept. 27. Vol. 55. No. 39. pp. 1635–1637. [19 refs.]

The authors treated 103 cases of malaria in Manila with plasmochin and plasmochin compound. Forty-three of the cases were pure *P. vivax* infections ; 37 *P. falciparum* infections ; twenty-three were mixed. Quartan infection is very rare in the Philippines. The conclusions reached are : (1) In agreement with Mühlens, a good parasiticidal effect was obtained with daily doses of 0·12 gm. of plasmochin in benign tertian, and with 0·06 gm. plasmochin and 0·75 gm. quinine sulphate in mixed infections, and in malignant tertian. (2) In double infections, where at first only one kind of parasite was found in the peripheral blood, pure plasmochin had a definite provocative action on *P. falciparum*, and plasmochin compound a provocative action on *P. vivax*. (3) It was noteworthy that in such cases pure plasmochin acted provocatively on both schizonts and crescents in *P. falciparum* infections, but plasmochin compound, on the contrary, only acted provocatively on the schizonts, never on gametes of *P. vivax*. (4) After administration of pure plasmochin the rings of *P. falciparum* acquired a certain degree of " tolerance," and were more difficult to destroy than

when plasmochin compound was given at once. Also when insufficient plasmochin was given a certain degree of resistance was noted. (5) Crescents may appear during the administration of plasmochin. (6) More or less severe toxic effects may occur, from cyanosis and pain in the stomach to severe hepatitis. (7) In their series they noted almost always marked cyanotic conditions, often with urobilin or urobilinogen in the urine, and comparatively slight stomach pains. (8) A specially severe toxic action on the white blood cells with the appearance of damaged marrow cells was noted as has been described in typhus fever, smallpox and pemphigus. (9) Because of its toxic action plasmochin should only be given under medical control. Its use as a prophylactic has not been established. It should be sold only on presentation of a prescription.

E. D. W. Greig.

DE MELLO (Froilano). Sur l'emploi de la plasmoquine dans le traitement du paludisme. [**The Use of Plasmoquin in the Treatment of Paludism.**]—*Presse Méd.* 1929. Sept. 18. Vol. 37. No. 75. pp. 1215–1217. [School of Med., Nova Goa.]

The author has employed plasmoquin in Goa with the same results that other observers have obtained elsewhere. It rapidly destroyed the gametocytes of all species of malaria parasites, and also the asexual forms of *P. vivax* and *P. malariae*. The red cells and the haemoglobin increased during treatment and the size of the spleen was diminished. Dr. de Mello concludes that plasmoquin has no action on subtertian schizonts, but that this difficulty can be overcome by giving quinine in addition. He found that toxic symptoms, such as pains in the stomach and cyanosis, quickly disappeared when the drug was stopped, but he recommends that it should not be given without medical supervision.

W. F.

WITTGENSTEIN (Annelise). Zur Chininempfindlichkeit der Impfmalaria. [**Quinine Sensibility of Inoculation Malaria.**]—*Deut. Med. Woch.* 1929. Nov. 22. Vol. 55. No. 47. p. 1959. [1 ref.] [III. Med. Polyclinic, Univ., Berlin.]

The author points out that inoculation malaria is much more sensitive to quinine than is malaria produced by the bite of a mosquito. From the observations recorded it is concluded that for the purpose of mitigating an attack of inoculation malaria the usual dose of quinine, from 0·1–0·2 gm., even the lowest limit, is too high. The author employs for the purpose pills containing 0·05 gm. quinine base. It is thought that spirocid might be preferable to quinine for mitigating an attack.

E. D. W. Greig.

DE LUCA (Benedetto). Lo stovarsolo e lo stovarsolo sodico nella cura della malaria. (**Stovarsol and Sodium Stovarsolate in Malaria.**)—*Riv. di Malariologia.* 1929. Sept.–Oct. Vol. 8. No. 5. pp. 569–584. [19 refs.] [English summary p. 634.]

During 1925–26 the author tested the effects of stovarsol and its sodium salt on 54 cases of unmixed infection with malaria, 30 benign tertian, 19 subtertian, and 5 quartan, and on 4 cases of mixed benign

and malignant tertian, and one of subtertian and quartan. The dose never exceeded 1 gm., and in nearly all was 0·75 gm. of stovarsol or 0·5 gm. of the sodium salt. The former was given orally only, the latter was tried intravenously also. Brief details of all the patients are given ; it was found that the drugs acted best on benign tertian, but even here they were not reliable, relapses being fairly frequent ; in subtertian and quartan they were even less effective and had no action on subtertian gametocytes. Though well tolerated by mouth, when given intravenously the results were at times severe headache, pain in the joints and albuminuria. These symptoms usually soon passed off and left no signs of permanent renal mischief.

H. Harold Scott.

Hooper (David). **On the Standardisation of Cinchona Febrifuge.**—*Quarterly Jl. Pharm. & Pharmacol.* 1929. Apr.–June. Vol. 2. No. 2. pp. 186–188.

An outline of the history of febrifuge, or quinetum, is given in this paper. The cinchona trees which were first cultivated in India were mostly *Cinchona succirubra* (red bark) and cinchona febrifuge was originally a mixture of the total alkaloids extracted from their bark. These trees were gradually replaced by other kinds richer in quinine, and the scarcity of red bark, in 1903 led to an alteration in the manufacture of febrifuge. Since that year it has been made from the alkaloids which remain after the extraction of the quinine from yellow bark trees. The author draws attention to the wide variations in the composition of different samples of the febrifuge ; " one would hesitate," he writes, " to render official a mixture of five alkaloids the proportion of which depends upon the exigencies of the cinchona plantations and the quinine factories." He agrees with Col. Gage, that a remedy may be found in a return to the cultivation of *C. succirubra* and the preparation of a febrifuge in large quantities from its bark.

W. F.

Fiorentini (Augusto). Nevriti e nevralgie sciatiche da malaria. (Patogenesi e contributo clinico.) [**Malarial Sciatica and Neuritis.**] —*Policlinico.* Sez. Med. 1929. Oct. 1. Vol. 36. No. 10. pp. 520–527.

[This paper is worthy of attention on account of the moral which it inculcates for those going out to practise in the tropics.] Three cases are recorded, two diagnosed as sciatic neuritis due to malaria, the third as neuralgia from the same cause.

[The connexion of the last with malaria is doubtful.]

The other two are more serious in their import ; they are fairly similar and the first only need be detailed. A man, 18 years of age, suffered from a prolonged bout of fever, with bronchial catarrh, meteorism, enlargement of spleen ; Widal negative. The blood smears showed sparse rings of *P. falciparum*. Two grams of quinine were injected hypodermically[!] on July 27th, and again on 29th ; the fever was continuous and remittent, so plasmoquine by mouth was given in addition on August 3rd ; after irregular intermissions the temperature reached normal on August 29th. On the 8th the daily dose of quinine had been reduced to 1·5 gm. and on the 22nd to 1·0 gm. till September 1st. On August 8th the patient complained of

pain along the sciatic, and three days later a gluteal abscess formed at the site of injection. The neuritis was severe and the reaction of degeneration in both muscles and nerve was present in September, and persisted as long as the patient remained under observation. [Comment is needless.]

H. Harold Scott.

Ullmann-Apostolon (Renée) & Apostolon (Georges). Traitement du paludisme chronique par le cacodylate de soude à hautes doses. [**The Treatment of Paludism with Large Doses of Sodium Cacodylate.**]—*Presse Méd.* 1929. Aug. 31. Vol. 37. No. 70. p. 1137.

The authors claim that the following treatment which is employed by them in Macedonia is a true specific for chronic paludism even of the worst type, and that it reduces the largest spleens to normal. As an authority for the use of such high doses they quote Professor Carnot & M. P. Ravaut.

On the first day of treatment, 0·5 cgm. of sodium cacodylate is injected intravenously, 1 mgm. of strychnine is given hypodermically, and 1·5 gram of quinine is given by the mouth. On the second day, the cacodylate is increased to 1 gram and the strychnine to 2 mgm. The quinine is continued throughout the treatment, and the strychnine may be increased if necessary. The treatment is continued until the seventh day, when the cacodylate is increased to 1·5 gram if there are no contra-indications. When 15 to 18 grams have been administered, the patient rests without treatment for 10 days. A second course is then given, followed by an interval of 20 days, and after this comes a third series, with a month's interval before a fourth. Four courses are usually sufficient to cure the patient, but should his spleen remain enlarged after an interval of three months, two or three additional courses should be given.

[This treatment cannot be free from danger. The average dose of sodium cacodylate is ½ to 1 grain or 0·03 to 0·06 gram. The maximum dose according to the French Codex is 3 grains or 0·19 gram in 24 hours.]

W. F.

Henry (A. F. X.). Séro-floculation palustre. Conditions d'observation, interprétation et discussion des résultats. [**Seroflocculation in Malaria. The Conditions to be observed, Interpretation and Discussion of the Results.**]—*C.R. Soc. Biol.* 1929. Aug. 13. Vol. 101. No. 25. pp. 1026–1029. [2 refs.]

The author insists that the greatest attention should be paid to details in making these tests. The results of ferro-flocculation should be read after three hours—2½ hours in the incubator at 37° C. and 30 minutes at room temperature. Flocculation or much opacity, in the control tubes, renders the reactions void. Melano-flocculation tests should be read after 2½ hours–2¼ hours in the incubator and 15 minutes at room temperature. An agglutinoscope is employed, and the tubes are gently reversed twice before reading the result. Only definite reactions are counted as positive. The author prefers a photometric method to simple macroscopic observation, and gives a formula for calculating the results. They are interpreted as follows :—

(1) Ferro-flocculation and melano-flocculation clearly positive. Almost certain malaria.

(2) One definitely positive and the other slightly positive. Almost always due to malaria.

(3) Both slightly positive. Doubtful.

(4) Dissociated reaction, one positive and one negative. Malaria is probable only if the positive reaction is very definite.

(5) Both negative. This result is inconclusive ; the test should be repeated when there is no fever, because the reaction sometimes becomes negative during an attack.

It is urged that in addition to making these serological tests the blood should be examined for parasites, the leucocytes should be counted, and the symptoms taken into account before the diagnosis is made. The melano-flocculation reaction is generally more sensitive than the ferro-flocculation reaction and it persists longer.

W. F.

Le Bourdellès (B.) & Liégeois (R.). Sur la mélanofloculation. Influence du temps de réaction. Les aspects du floculat en eau distiliée et eau salée ; leur signification. [**Melano flocculation. The Influence of Time on the Reaction. The Appearance and Significance of Flocculation in Water and in Salt Solution.**]—*C.R. Soc. Biol.* 1929. Aug. 13. Vol. 101. No. 25. pp. 1148–1149. [2 refs.]

In a former communication the authors reported (see this *Bulletin*, Vol. 26, p. 941) 25 per cent. of positive reactions in non-malarious controls with Henry's melano-antigen. These reactions were slow, almost always limited to the tubes containing distilled water, and accompanied by a negative ferro-flocculation. The readings were taken at the end of four hours. In a new series they have obtained satisfactory results by shortening the time to three hours as recommended by Henry, and they now consider the reaction of the greatest diagnostic value. They point out that positive sera which give a dull white or light brown flocculation in the distilled water tubes often give a dark brown or black flocculation in the saline tubes. These shades are best seen in reflected artificial light. The authors conclude that melanin plays an active and probably antigenic part in the reaction.

W. F.

Le Bourdellès (B.) & Liégeois (R.). Le séroflocculation du paludisme (réaction de Henry) ; son intérêt clinique. [**Seroflocculation in Malaria (Henry's Reaction) : its Clinical Importance.**]—*Bull. et Mém. Soc. Méd. Hôpit. de Paris.* 1929. Oct. 28. Year 45. 3rd Ser. No. 27. pp. 1198–1202. [2 refs.]

The authors state that the theory on which Henry bases his reaction (see this *Bulletin*, Vol. 26, pp. 940–942) is as follows : In addition to the antigens which are introduced into the body from without—the " exo-antigens "—there are also antigens produced within the body in response to various stimuli. These he calls the " endo-antigens " or " endogenes." The endogenes determine the formation of antibodies—the " anti-endogenes." The endogenes of malaria are the malarial pigments, and, in order to detect the presence of their anti-endogenes, Henry employs homologous antigens prepared from choroidal pigment and from organic iron salts, which produce specific flocculation when in contact with malarial serum. These flocculations are called, respectively, " melano-flocculation " and " ferro-flocculation."

The authors give the results of flocculation tests in 400 cases, which they divide into five categories.

(1) *Examined during an attack of malaria*, 58 *cases*. Patients who were therapeutically inoculated with malaria gave negative reactions during the incubation and during the initial stages of the fever, but when the attack was in full swing the reaction always became positive.

(2) *Old cases of malaria with enlarged spleens*, 37 *cases*. Melano-flocculation was constantly positive; ferro-flocculation was positive in 20.

(3) *A similar group but without enlarged spleens*, 37 *cases*. Melano-flocculation was positive in 16, and ferro-flocculation in 10.

(4) *A group of men who had been infected some ten years before, and who were immediately repatriated and treated with quinine*, 82 *cases*. The results were almost all negative.

(5) *A control group consisting of* 88 *healthy persons and* 122 *who were suffering from various diseases*. The results were generally negative if the results were read at the end of three hours, as recommended by HENRY. HENRY states that the reaction is positive in haemocyto-clastic diseases, and the authors found it positive in a case of syphilis. They consider that it should be employed to regulate the quinine treatment of malaria in the same way as the Wassermann reaction is used to regulate the salvarsan treatment of syphilis.

W. F.

STRICKLAND (C.). **The Relative Malarial Infectivity of Some Species of Anophelines in Cachar (Assam).**—*Indian Jl. Med. Res.* 1929. July. Vol. 17. No. 1. pp. 174–182. [3 refs.]

This study is supplementary to Dr. Strickland's Report on Malaria in the Duars Tea-Gardens (see this *Bulletin*, Vol. 26, p. 909). Mosquitoes to the number of 10,000, caught mostly by trapping between April and December 1927, were identified and dissected by five specially trained laboratory assistants. The results were as follows: *A. funestus*, caught 1,489; infected 58. *A. Vagus*, caught 1,341; infected 1. *A. karwari*, caught 1,697; infected 1. *A. philippinensis*, caught 2,410; infected 0. *A. hyrcanus*, caught 1,757; infected 0. Dr. Strickland concludes that the "experiment has definitely confirmed the enormous relative importance of *funestus* in the malaria problem of the Assam tea-gardens."

W. F.

AVERBOOKH (J.). **To the Study of the Consequence of the *Anopheles pulcherrimus* in the Malaria's Etiology.**—*Pensée Méd. d'Usbékistane.* Tashkent. 1928. Feb. No. 5. pp. 21–25. [4 refs.] [In Russian. English summary p. 92.]

The author fed 12 specimens of *A. pulcherrimus* on malaria patients, with the result that zygotes appeared in 5 of the mosquitoes, but he did not succeed in conveying the infection to other persons. When these anopheles are fed on patients with *P. vivax* in the blood, zygotes appear about 8 days later, and sporozoöites after about 14 days, if the mosquitoes are kept at a temperature of 26° to 30° C.

W. F.

Steinfeld (Fritz). Uebertragungsversuche von Menschenmalaria auf Affen. [**Experiments to transmit Human Malaria to Monkeys.**] —*Arch. f. Schiffs- u. Trop.-Hyg.* 1929. Nov. Vol. 33. No. 11. pp. 592–594. With 2 text figs. [Inst. for Ship & Trop. Diseases, Hamburg.]

Two monkeys, whose spleens had been removed, received intravenously and subcutaneously human malaria (*P. malariae* and *P. falciparum*). The blood of the monkeys was examined daily, but remained free from parasites. In the quartan monkey a pigmented leucocyte was found. Adrenalin provocation was without result. In the monkey infected with *P. falciparum* the R.E. system was blocked before the third inoculation of blood to lower resistance. The quartan monkey died on the 12th day from an unknown cause. No parasites were found in the internal organs. The only positive result was the finding of pigment in the kidney and liver.

E. D. W. Greig.

Ruge (Heinrich), Lohfeldt, Knabe, Eisenberg & Kunert. Beiträge zur pathologischen Physiologie der Malaria. (Untersuchungen ueber das Verhalten des Blutzuckers, des Reststickstoffes sowie der Nieren- und Magenfunktion.) [**The Pathological Physiology of Malaria.**]—*Arch. f. Schiffs- u. Trop.-Hyg.* 1929. Nov. Vol. 33. No. 11. pp. 567–587. With 15 text figs. & 14 charts. [Inst. for Ship & Trop. Diseases, Hamburg.]

The cases which formed the subject of this investigation were chiefly amongst seamen who were suffering from active malaria or had previously passed through an attack. The stimulus to start the investigation arose from the observation that stomach troubles are comparatively frequent amongst those who had acquired malaria during the war and had been treated with quinine. All three varieties of malarial infection were represented in the cases. The investigations comprised: (1) The estimation of the blood sugar in 140 cases. (2) Estimation of the non-protein nitrogen in 143 cases. (3) Water estimations in 60 acute cases and 30 old cases. This estimation was made by giving 1,500 cc. tea and noting the amount and specific gravity of fluid excreted in the first six hours; it was reckoned that 1,500 cc. ± 10 per cent. should be excreted in this time. (4) Estimation of the stomach function: (*a*) by chemical investigation; (*b*) X-ray examination. The authors conclude from their investigations: That an increase of blood sugar only occasionally occurs in malaria. It does not exceed 130 mgm. per cent. The non-protein nitrogen during the fever period reaches the upper normal limit. In uncomplicated cases of malaria 40 mgm. per cent. are rarely exceeded, still less frequently after cessation of the fever and disappearance of parasites. The water estimations show that in about three-quarters of the cases investigated there is a certain delay in excretion associated with good concentration. Two cases of blackwater fever gave a very delayed excretion and once the non-protein nitrogen reached 48 mgm. per cent. The influence of residence in the tropics, quinine, etc., is seen in the results of the chemical investigations of the stomach. They found in about half to two-thirds of the cases hypo- or achlorhydria [this is interesting in relation to sprue] and one-fifth have hyperchlorhydria. The X-ray examination did not show any pathological alterations in the stomach in malaria.

E. D. W. Greig.

HORN (Ludwig) & KAUDERS (Otto). Ueber das Verhalten der Parasiten bei der Impfmalaria unter den besonderen Bedingungen der Malariablutkonservierung und der latenten Malariainfektion. [**Behaviour of the Parasites of Inoculation Malaria in Preserved Blood and Latent Malarial Infection.**]—*Ztschr. f. Parasitenk.* 1929. Oct. 12. Vol. 2. No. 2. pp. 178–212. With 15 figs. (3 coloured). [22 refs.] [Psychiat. Clinic, Univ., Vienna.]

This investigation was carried out by the authors in the clinic of Professor WAGNER-JAUREGG. The changes in morphology of the *P. vivax* were noted in blood from patients inoculated with malaria and preserved in various ways, viz., citrated; in blood agar; blood mixed with gelatine; blood alone; preserved in the ice chest, at room temperature, in incubator at 37° C.; defibrinated blood. The observations on latent malarial infection were made by examining the parasites in patients who had received a second inoculation of malaria and in whom a fever-free interval occurred; although the fever had subsided, yet the blood was proved to be infective by inoculation into another patient. Further, if the serum of such a patient with a latent infection be injected immediately after an intravenous injection of malarial blood a similar fever-free or latent malarial infection is produced. The authors give full details of the very careful observations. From a consideration of their results they reach the following conclusions. Under the altered biological conditions of preservation and latent infections the parasites change into extraglobular, round, gamete-like structures, which are morphologically indistinguishable from true gametes. It is known that the sexual forms of the malarial parasite are the least susceptible to unfavourable conditions, such, for example, as the administration of quinine. They regard the production of gamete-like round bodies as a degeneration process, but when they are replaced in favourable conditions they are capable of living and producing fresh infection. The action of quinine on the parasites will form the subject of a further investigation. The morphological changes described are illustrated in 15 microphotographs.

E. D. W. Greig.

SIRCA (Antonio). Comportamento della riserva alcalina del sangue nei bambini malarici. [**The Blood Alkali Reserve in Children with Malaria.**]—*Pediatria.* 1929. Sept. 1. Vol. 37. No. 17. pp. 947–951. [13 refs.] [Inst. Clin. Pediatrics, Univ., Sassari.]

BOSISIO had estimated the alkali reserve in adults with malaria, but the author, examining the same in fifteen children, all of whom were proved to have malarial parasites in the blood, arrived at somewhat different results. During an acute febrile access the reserve is lowered, as had been recorded by BOSISIO in adults, but during the apyrexial period it was found to be normal. In chronic cases with enlarged liver and spleen and marked anaemia he found the reserve very high, whereas BOSISIO in adults had found it normal.

H. Harold Scott.

POTAPENKO (N. A.). [Die osmotische Resistenz der Erythrocyten bei Malaria.] [**Osmotic Resistance of Red Cells in Malaria.**]—*Russian Jl. Trop. Med.* 1929. Vol. 7. No. 4. pp. 234–239. [In Russian. German summary pp. 239–240.]

The work was carried out during 1925 and 1926 at the Malaria Station of Dnjepropetrovsk [Russia]. In all 140 cases were investigated. [Nature of

the malarial infection is not specified in the summary.] In order to study the relationship of osmotic resistance of red cells to the clinical course of malaria, patients were grouped into those running: (1) A severe course with complications. (2) An ordinary course with complications. (3) An ordinary course without complications. In all three groups there was a typical lowering of the minimal osmotic resistance of red cells. The maximal resistance varied little in the three groups.

E. D. W. Greig.

Porto Rico. Report of the Commissioner of Health to the Governor of Porto Rico for Fiscal Year ending June 30, 1927. pp. 62–95.—**Report of Bureau of Malaria Control 1926-27.**

Malaria in Porto Rico is intimately associated with the irrigation of sugar-cane fields and with tidal swamps. The two common species of anopheles are *A. albimanus* and *A. grabhami*. Control measures have been undertaken in limited zones round the towns and villages; the main practice adopted was to drain whatever could be drained, and to apply Paris green—1 per cent. in powdered limestone—to the remainder at weekly intervals. Automatic tide gates were found most useful in the lowland fields near the coast; when fresh water (? a fresh supply of sea-water) was kept out by their use, a scum formed on the surface and larvae failed to develop. Screening of houses is widely used in Porto Rico, but the screens are quickly destroyed by the salt-laden air. Several materials have been tested; cloth screens kept out the air and they rotted very quickly; bronze screens and copper screens outlasted galvanized iron, but for use near the sea the "Model" metal of the American Wire Fabric Co. appeared to be the best. There appeared to be no advantage in using a screen with a mesh finer than that needed to keep out mosquitoes, because "the small biting flies seem to be able to pass through anything that air will pass through." Screening was found preferable to mosquito nets. Observations were made on the feeding habits of *A. albimanus* and *A. grabhami* in order to discover whether they prefer to feed on men or on domestic animals. For this purpose, men were placed in a specially built house and various animals were tethered close to the entrance. The mosquitoes subsequently caught in the house were examined by precipitin tests to determine the source of the blood in their stomachs. *A. grabhami* preferred animals to men, and it was found that the proximity of horses or oxen afforded considerable protection when they were placed between the men and the breeding-places of the mosquitoes. It was concluded that "whether people will be bitten or not will depend upon the proximity and position of the animals with relation to the breeding-places and the direction of the wind."

W. F.

Gross (R. D.). **Effectiveness of Antimalaria Measures in Rural Singapore.**—*Malayan Med. Jl.* 1929. Sept. Vol. 4. No. 3. pp. 91–92.

The annual report for Singapore showed that there were as many deaths from malaria in 1928 as there were before anti-malaria work in rural areas was commenced. The author attributes this to the influx of infected immigrants from China and Johore, to the lack of hygienic precautions on small native estates, and to the opening up of large areas of forest by Chinese squatters who settle themselves on the land

while jungle-felling is in progress and before any oiling or other anti-malaria measures can be undertaken. In established villages where anti-malaria work has been carried out, there has been a great reduction of infection; for example, before work was commenced in 1921, the spleen rates of three of these villages were, respectively, 39·6, 26·3, and 62·5, as compared with 3·6, 1·02 and 7·3 in 1928.

W. F.

EJERCITO (Antonio). **Summarized Report on Malaria Surveys and Control in Mindanao and Sulu.**—*Jl. Philippine Islands Med. Assoc.* 1929. Aug. Vol. 9. No. 8. pp. 277–283.

This paper deals with malaria control by anti-larval measures directed against the principal Philippine carrier, *Anopheles minimus*. The method adopted was weekly hand-spraying with 1 per cent. Paris green, mixed with road-dust which had been passed through a 60-mesh screen. The Paris green consisted of spherical crystals (not amorphous powder) of 8 to 20 microns diameter, and it contained a minimum of 50 per cent. of arsenious trioxide. In addition to *A. minimus*, the following anopheles were found: *maculatus, barbirostris, hyrcanus, rossii* (*vagus*), *rossii* (*subpictus*), *aitkeni* (1 and 2), *ludlowi, umbrosus*, and an unidentified anopheles which the author describes; he considers that it is a new species.

W. F.

BARBER (M. A.) & KING (C. H.). **Some Notes on the Limitations of Screens in the Prevention of Malaria.**—*Public Health Rep.* 1929. Mar. 8. Vol. 44. No. 10. pp. 523–528. With 2 plates.

An interesting note on prevalent and increasing malaria in a place where screening was common and reasonably thorough. Investigation seemed to show (1) that staying out after dusk and even sleeping out negatived the protection of house screening, and (2) that imperfect screening, far from being worse than useless as is commonly said, did exclude anopheles from the houses to an appreciable extent. In places where anopheles are accompanied by the savage biting mosquitoes, screening is likely to be specially helpful because taken advantage of: "the evening air fortified by such a pungent ingredient as *Aëdes sollicitans* may well become unbearable."

J. F. C. H.

MANSELL (R. A.). **An Experiment in the Prophylaxis of Malaria.**—*Jl. Roy. Army Med. Corps.* 1929. Feb. Vol. 52. No. 2. pp. 110–112. With 1 fig. [2 refs.]

The experiment concerned troops moving from the plains to the hills and *vice versa* at mid-season. It had been observed that both parties of troops regularly, year by year, became heavily infected at certain camps in the foothills where they halted during the change over.

Mansell had remarked the observation of YORKE (this *Bulletin*, 1926, Vol. 23, p. 148) that 10 grains of quinine given before, on the day of and for 7 days after an infective feed did not prevent the development of malaria and that the amount of quinine given in such a way was immaterial.

He gave his men 15 grains of quinine twice daily for 8 days, commencing a week after quitting the malarious camps. The result of the first year's trial seems to justify the procedure, there having been a much diminished morbidity from malaria. J. F. C. H.

MANSELL (R. A.). **Some Answers to the Cantonment Antimalaria Problem.**—*Jl. Roy. Army Med. Corps.* 1929. Sept. Vol. 53. No. 3. pp. 196–201. With 1 chart in text.

During recent years two lakhs of rupees have been allotted annually in army budgets for antimalaria work in cantonments. In support of this expenditure, the author gives graphs and tables showing the rapid and definite fall which has taken place " in one of the most malarious districts in the north of India " since these funds have been available. He states that in four years there has been a saving of 3,287 admissions of British and 1.908 Indian troops to hospital against an expenditure of 1½ lakhs of rupees ; though he admits that this reduction may have been not wholly due to antimalaria measures.

W. F.

PARSONS (Albro L.). **Malaria Control at Camp Stotsenburg, P.I.**—*Milit. Surgeon.* 1928. Dec. Vol. 63. No. 6. pp. 816–829. With 2 charts. [1 ref.]

This article emphasizes the well-known fact that however well troops are protected against malaria in their permanent quarters, the exigencies of military service in a malarious area, whether the service be active warfare or peace-time exercises, make it practically inevitable that numerous infections will take place.

The study is notable because it reveals considerable confusion in the classification of the anopheles of the area concerned and consequent difficulty in determining the dangerous species.

One would have liked to know the incidence of the three types of malaria, but the only information is that 1927 was a typical year when " all admissions were for tertian malaria save four aestivoautumnal. Only very occasionally do we find quartan malaria."

Paris green has been used with good effect, but regarding prophylactic quinine " the belief has gained ground that the daily dose of quinine, while keeping the soldier on his feet, in reality only serves to delay his illness—prolong the incubation period." J. F. C. H.

MOSCHKOWSKI (Sch.). Ueber Chininprophylaxe bei Malaria. [**Quinine Prophylaxis in Malaria.**]—*Arch. f. Schiffs- u. Trop.-Hyg.* 1929. Nov. Vol. 33. No. 11. pp. 555–566. [Refs. in footnotes.] [Trop. Inst., Moscow.]

The author describes his method of discontinuous prophylactic quininization. The chief questions for consideration are : (1) The sequence of quinine days ; (2) the time for administration ; and (3) the dose. As regards the first, he recommends administration on two successive days with three days' interval ; secondly, the quinine is to be given in the early morning ; and thirdly, a moderate therapeutic dose (0·4–0·5 gm.) is indicated. An opportunity of trying out in practice the author's views was afforded in the extensive investigations carried out since 1924 in various districts of the Soviet Republic.

Thus in the summer of 1924, 15,000 soldiers received quinine prophylactically. Amongst the quininized (of which only 66 per cent. regularly received quinine) 11 per cent. became sick during the malaria season, whilst in the non-quininized group, which was in a favourable area, the percentage of sick was 5 times as great. 60 per cent. of the soldiers received the quinine according to the author's scheme in the early morning, the remainder receiving it daily towards the evening. Amongst 1,500 soldiers who had never previously suffered from malaria and were treated prophylactically according to the author's scheme, 5·2 per cent sickened, whilst in a group of similar strength receiving quinine daily towards evening the sick rate was 6·4 per cent. No great difference, but the advantages of the author's scheme were brought out in other groups, in which only 8 per cent. sickened in course of the malarial season, whilst the number of attacks amongst those treated by the other method was 34 per cent. during the malarial season. Other investigatons are recorded. He selected his method on theoretical grounds, after considering all possible combinations; he believes that his scheme of discontinuous administration is the most satisfactory, as the attacks (sporulation of the parasite) fall on fewer quinine-free days than in the other system. He considers that the investigations, carried out under various conditions during the years 1924–1928, favour quinine prophylaxis in general and his method in particular.

E. D. W. Greig.

Jamot (E.). Note sur des essais de quininisation préventive et curative au Cameroun. [**Prophylactic and Therapeutic Quininization in the Cameroons.**]—*Bull. Soc. Path. Exot.* 1929. July 10. Vol. 22. No. 7. pp. 555–568.

The inhabitants of 8 villages, numbering 2,424 persons, were examined with the result that parasites were found in 51 per cent.; about half the infections were due to *P. falciparum*. In children under 15 the parasite index was 75 per cent.; in adults it was about 43 per cent. These figures are interpreted to mean that practically everyone was infected. In order to gauge the value of prophylactic quinine in such a population, 586 persons, found free from parasites at the preliminary examination, were given various doses at different intervals. At the end of a fortnight they were re-examined, with the result that 78, or 13 per cent., were found to harbour parasites. At the end of four weeks they were examined again, and parasites were found in 20 per cent. The results in a control group of 582 who received no quinine were in marked contrast. In this group parasites were found in 247, or 42 per cent. a fortnight later, and in 55 per cent. at the end of a month. The author found that the results of giving a prophylactic dose of 1 gram of quinine every 7 days were as good as those which followed daily doses of 0·25 and 0·5 gram.

W. F.

Missiroli (A.). Versuchsstation für den Kampf gegen Malaria. Zur Präventivbehandlung mittels Schweinfurtergrün in der Praxis. [**Prevention of Malaria by Paris Green.**]—*Seuchenbekämpfung*. Vienna. 1929. Vol. 6. Nos. 3 & 4. pp. 155–161; 238–244. With 5 text figs.

The work was carried out chiefly at Portotorres in Sardinia and Bianconovo in Calabria. Later it was extended to other parts. In

the first paper the author describes the method of using Paris green as a larvicide. The description is continued in the second paper, which gives also the spleen and parasite indices; these were :—

	Spleen.				Parasite.			
	1924	1925	1926	1927	1924	1925	1926	1927
Bianconovo ...	56·2	54·2	29·2	21·3	17·8	10·3	0·45	0·47
Portotorres ...	46·8	42·4	27·0	27·4	34·2	8·7	5·9	5·5

Operations were commenced in 1925. From this table it is apparent that in two years malaria in Bianconovo has completely disappeared and has rapidly receded in Portotorres. These results are supported by those obtained in other countries where antilarval campaigns with Paris green have been carried out. The antilarval campaign with Paris green can be carried out in the poorest Italian districts. The costs are low.

E. D. W. Greig.

Businco (Ottavio). Le gastro-enteropatie dei malarici cronici. (Sintesi radiomorfologica e patogenetica.)—*Riforma Med.* 1929. Aug. 24. Vol. 45. No. 34. pp. 1142, 1145–1147. [4 refs.] [Inst. of Path. Anat., Univ., Cagliari.]

Ejercito (Antonio). Plasmochin and Quinine in the Prophylaxis and the Prevention of Malaria Relapses.—*Jl. Philippine Islands Med. Assoc.* 1929. July. Vol. 9. No. 7. pp. 229–234.

Guerra Méndez (R.). El signo de Pagniello en el paludismo.—*Gac. Méd. de Caracas.* 1929. (25° Aniv. Acad. Nac. de Med. Numero extraord.) pp. 69–70.

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SLEEPING SICKNESS.

League of Nations. Health Organisation. **Report of the Second International Conference on Sleeping Sickness held in Paris, November 5th to 7th, 1928.** C.H. 743.—90 pp. With 3 maps in text. 1928. Geneva.

The first portion of this report describing the constitution of the Conference and the recommendations adopted has already received notice [this *Bulletin*, Vol. 26, p. 185].

The next section consists of an address by Mr. Ormsby-Gore, who, after expressing the pleasure of the British delegates in accepting the invitation of the French Government for the Conference to meet in Paris, briefly outlined the present position as regards trypanosomiasis in the various British Colonies in Africa. He referred to the important administrative work which has been done in the Sudan and is now being commenced in Uganda, in regard to the administrative control of African natives threatened with infection, by control of their movements, by the issue of medical passes and the like. For reasons which he mentions no one method can, however, be universally applied, but each administration faced with the problem has much to learn from the experiments carried out by its neighbours. This is true not merely between territories under the administration of different European Powers, but even between different British administrations. Mr. Ormsby-Gore concludes as follows :—

" If I were asked to sum up what is the main contribution which Europe has henceforward to give to the solution of the problems of the tropics, now that the reign of peace and law has been established, I should say that it is in one sphere of knowledge—bionomics—a knowledge of the laws of life.

" I take it that the chief object of this Conference is to discuss together how best we can advance our still restricted knowledge of these laws of life by further research and by practical administrative action based upon such limited knowledge as we already possess."

The third section is a report submitted by the Belgian Ministry of the Colonies on trypanosomiasis in the Belgian Congo. A table is given showing the number of persons examined, and of those punctured, and also of the new cases, old cases, and cases under treatment in the various provinces. This is followed by a brief analysis of the state of affairs in each province. As the work referred to has already been published in various articles which have been summarized in this *Bulletin* further reference is unnecessary.

The fourth article is a memorandum submitted by the British Colonial Office. A brief and interesting summary is given firstly of the tsetse fly investigation going on in Nigeria and Tanganyika, and secondly, of the results obtained in the treatment of cases of sleeping sickness by various workers with various drugs in different parts of Africa. The last portion of the British memorandum consists of a summary of the condition of sleeping sickness questions in various British Colonies and protectorates in 1925, and the progress made in that and the following years. The papers on which this memorandum is based have all received notice in this *Bulletin*.

The fifth article deals with sleeping sickness in the Sudan.

The sixth is entitled " A Report submitted by the Inspector-General's Office of the Public Health Service of the Ministry of the Colonies of

the French Republic: Campaign against Sleeping Sickness in the French Colonies and Mandated Territories (Togoland and the Cameroons)." This report describes the present organization of the service and the methods employed to stamp out sleeping sickness; it concludes with a résumé of the experiments carried out in recent years at the Brazzaville Pasteur Institute in the treatment of sleeping sickness mainly with tryparsamide and 'Fourneau 270.'

The final section is a report by the Directorate-General for Morocco and the Colonies of Spain (Spanish Guinea and Fernando Po).

W. Yorke.

JAMOT (E.). La maladie du sommeil au Cameroun en janvier 1929. [**Sleeping Sickness in Cameroon in January 1929.**]—*Bull. Soc. Path. Exot.* 1929. June 12. Vol. 22. No. 6. pp. 473–496. With 1 coloured folding map.

The mission created in July, 1926, to combat sleeping sickness had as its first objective the precise determination of the extent of the disease. Eight expeditions comprising 150 native orderlies and 70 microscopes and directed by European doctors have devoted two years to this work, and the results of their labours form the subject of the present paper, which deals especially with the foci in the centre, the east, the south and the south-east of the territory.

The distribution of the disease is shown in an excellent map. The area of the infected territory is approximately 80,000 square kilometres and the population is about 800,000, that is about 10 per kilometre; but certain districts are almost without population, so that in the truly inhabited districts the population is much denser. A brief account is given of the nature of the country and of the vegetation.

The disease is by no means evenly distributed throughout the whole of this vast area; in some places its incidence is very great and in others but slight. The author has divided the area into (1) endemic zones in which the number of infected does not exceed 15 per cent, (2) epidemic zones where it is definitely above 15 per cent., and (3) endemo-epidemic zones where the coefficient of infectivity is sometimes below 15 per cent. and sometimes above this figure. The position and size of these various zones is clearly shown in the map. A detailed description of the state of affairs in each of the zones is given.

The next portion of the report deals with results of treatment: the patients are divided into the following four groups:—

1. Old cases in good state without trypanosomes in the blood.
2. Old cases in good or bad condition with parasites in the blood.
3. New cases.
4. Old or new cases in very bad condition.

All the cases, whether new or old, are treated locally.

The drugs mainly used were atoxyl and tryparsamide, and during the years 1927 and 1928, 900 kgm. of atoxyl and 600 kgm. of tryparsamide have been injected in the Cameroons. The old cases have received one or more series of 6 injections of atoxyl or of 10 injections of tryparsamide. In certain very heavily infected villages, the healthy have also been atoxylized. Atoxyl has been usually given subcutaneously in doses of 1·5 cgm. to 2·0 cgm. per kilo., repeated every 10 to 14 days. Tryparsamide was given intravenously in 20 per cent. solution, or

subcutaneously in 10 per cent. solution in doses of 4·5 cgm. per kilo. at weekly intervals. As a rule, the latter drug was reserved for severe cases.

The old cases with parasites in the blood were given novarsenobenzol, emetic, moranyl or tryparsamide or combinations of these drugs.

Atoxyl. The patients treated with this drug received a large dose immediately the diagnosis was made and during the following 3 months a series of 5 or 6 similar injections. Information is given regarding the results obtained in Lomié, where 7,664 patients received this treatment and in Abong-Mbang where 5,516 patients were given it.

Tryparsamide. In the course of the second half of 1926, the use of tryparsamide was commenced in the camp of Ayos and it was given systematically in the hospital, but it was only towards the middle of 1927 that the drug was employed for the treatment of patients in the bush.

In June, 1927, it appeared that the Djem tribe which lives on the road from Abong-Mbang to Lomié, and where DE MARQUEISSAC in January, 1926, found 84 per cent. of the population to be infected, was being exterminated. Of the 2,220 inhabitants found in 1923 only 642 remained and of these 540 were infected. All of these patients, the majority of whom were in a very bad state, had received some months previously a final series of 6 injections of atoxyl, but this was powerless to arrest the mortality. Jamot ordered 10 injections of tryparsamide for each infected person and 5 injections of atoxyl for each healthy person. This treatment arrested the mortality and restored it to normal dimensions.

In the other tribes of Abong-Mbang, the patients in good condition were given atoxyl, and those in bad condition a series of 10 injections of tryparsamide. Up to November 1st, 1928, 25,638 patients had benefited by treatment with tryparsamide.

Referring to the accidents resulting from the use of tryparsamide, Jamot states that of the 135,186 subcutaneous injections of the drug only 284 were followed by abscesses. He adds that provided proper aseptic precautions are taken abscesses never occur.

Of the 25,638 patients treated with the drug 233 (0·8 per cent.) developed occular troubles. As a rule, these were transient, but in 30 there was persistent amblyopia and in 17 definite amaurosis. The accidents may follow the use of too large doses in advanced cases, and the author believes that it is important to use distilled water in the preparation of the solution for injection ; if the solution is not perfectly clear it should be rejected.

The results of treatment with tryparsamide are summarized in a table.

Various attempts at preventive treatment were undertaken. In a very heavily infected region the experiment of BOSSUET and DE TRÉVISE was repeated ; the results, which appear to be negative, will be communicated in a later paper. On the contrary, interesting results have been obtained through atoxylization of the healthy in heavily infected villages. In the villages on the road from Abong-Mbang to Djaposten, where the scourge is exceptionally severe, 1,561 healthy persons have each been given 5 large doses of atoxyl at 14-day intervals, whilst the patients in the same villages were treated with tryparsamide. Between 2 and 9 months later BAUGUION revisited the villages and found that of the 1,561 atoxylized 74 (4·8 per cent.)

were infected, and of the 63 who were not atoxylized 33 (52·3 per cent.) were infected. Similar observations were made elsewhere.

The paper closes with a discussion of the effect of treatment on the death rate and birth rate.

W. Y.

BUCHANAN (J. C. R.). **Note on the Trypanosome Infection Rate of Wild Game.**—*Kenya & East African Med. Jl.* 1929. July. Vol. 6. No. 4. pp. 111–113. [6 refs.]

The observations recorded in this note were made in the Rukwa Valley, an epidemic centre of Rhodesian sleeping sickness in the Ufipa district of Tanganyika. Microscopic examination was made of the peripheral blood of 150 animals : the thick drop method was used in every case, but in addition, wherever possible, thin films were used for the identification of the parasites. Subinoculations into laboratory animals were not made. Details are given in tables. Of the 150 animals examined, 31 (20·7 per cent.) were found to be infected. In 18 of these the infection was probably *T. brucei*. Waterbuck appeared to be the most frequently infected, 18 of the 33 examined being found to harbour trypanosomes in the blood.

W. Y.

BUCHANAN (J. C. R.). **Some Clinical Aspects of Trypanosomiasis rhodesiensis.**—*Trans. Roy. Soc. Trop. Med. & Hyg.* 1929. June 25. Vol. 23. No. 1. pp. 81–88. [6 refs.]

During analysis of a series of 49 consecutive cases of Rhodesian trypanosomiasis, the author was impressed by a great variation in symptomatology and in types of the disease. There appeared to be certain clinical points which had not previously been emphasized. The principal symptoms recorded in the complete series are summarized in a table, which shows at a glance how greatly toxic manifestations predominate over signs referable to central nervous system involvement. This might be taken to imply that, as in the case of *T. gambiense* infections, the central nervous system becomes invaded late in the course of the disease. It is, however, generally recognized that such is not the case, and the findings in ten individuals, whose cerebrospinal fluids were examined within three weeks of the first onset of symptoms, show how really early in the course of the disease this may occur. The condition of the cerebrospinal fluid at the beginning of the illness in these ten individuals is shown in a table. All had greatly increased cell count and in five of the ten trypanosomes were actually found.

Rapid emaciation, weakness, pain and oedema were probably the most obvious signs of toxic action resulting from the trypanosome infection, but a careful observation of the condition of the heart in a series of 74 unselected cases show that there was an important effect on the cardiac system. Of the abnormalities found, irritability, causing an instability of the pulse rate and a degree of tachycardia quite out of proportion to the pyrexia present, was by far the most common. All degrees of cardiac disorder were observed, from simple loss of tone and subsequent weakness of the sound to complete disorganization of rhythm and heart failure.

The author was able to classify his cases into three distinct clinical types. In the first, the disease began suddenly and ran a dramatically

acute course, ending fatally in two or three months in untreated cases. In the second, the onset of the disease was insidious and the course was chronic; in an extreme instance it lasted for some years. The third type, of which only two cases were seen, was characterized by an acute onset with little systemic disturbance, but with symptoms and lumbar puncture findings which proved grave pathological changes to have taken place in the central nervous system.

The author considers that two factors must determine the type of the disease which will develop in any particular case, viz., individual resistance and virulence of the infecting trypanosomes. The paper concludes with a discussion of these two factors.

W. Y.

Regendanz (P.) & Hoeppli (R.). Die Einwanderung der Trypanosomen in das Gewebe und die dadurch bewirkten histopathologischen Veränderungen. [**The Migration of Trypanosomes into the Tissues and the Histopathological Changes produced.**]—*Arch. f. Schiffs- u. Trop.-Hyg.* 1929. July. Vol. 33. No. 7. pp. 376–387. With 4 text figs. [11 refs.] [Inst. for Ship & Trop. Diseases, Hamburg.]

After briefly reviewing the literature of this subject, the authors pass to a description of the histopathological changes found by them in the heart of monkeys, the eyes of rats, and the brain of a hamster infected either with *T. gambiense* or *T. rhodesiense*.

The following are the conclusions :—

1. The histological changes in the hearts of monkeys infected with *T. gambiense* and *T. rhodesiense* are described; they relate to pericarditis and myocarditis produced by the trypanosomes.

2. The trypanosomes present in the pericardial fluid cause an inflammation of the pericardium and subsequently inflammation of the heart muscle, which is accompanied by marked increase of fluid between the muscle bundles. After such damage to the epicardium it is possible for the parasites to wander into the tissue; here they multiply and produce definite damage to the tissue.

3. Trypanosomes can wander into the anterior chamber of the eye and multiply there. As a result changes appear in the cornea, iris, and lens. These changes are accompanied by oedema and inflammation of the conjunctiva.

4. The trypanosomes wander out of the fluid in the anterior chamber into the inflammatory oedema of the conjunctival tissue and finally appear in the conjunctival sac.

5. In the fluid of the conjunctival sac living trypanosomes may be found in great numbers when they are present in only scanty numbers in the peripheral blood.

W. Y.

Graf (H.). **Report on Four Cases of Trypanosomiasis occurring in Europeans of the British Cameroons.**—*Trans. Roy. Soc. Trop. Med. & Hyg.* 1929. June 25. Vol. 23. No. 1. pp. 95–100. [1 ref.]

Notes are given of four cases of sleeping sickness, all of which presented unusual features. In each case, the Glossina bite which initiated the disease was accompanied by marked constitutional disturbances. None of the patients had actually felt the bite, but in all four the external appearances of the swellings clearly pointed to an

insect as the cause. Case I is particularly interesting in that it occurred in a European, who was on his first visit to the Tropics, and who had arrived in the Cameroons only two weeks prior to the bite which, in the author's opinion, was the undoubted cause of the infection; marked constitutional disturbances occurred immediately after and continued unabated until the appearance of the secondary symptoms. In Case 2, the author succeeded in demonstrating the presence of trypanosomes in the actual lesion produced by the bite. In three of the cases, trypanosomes were found in the blood stream within a few days of the bite that apparently initiated the disease. Unfortunately, the author was unable to decide whether the parasite in these cases was *T. gambiense* or *T. rhodesiense.*

W. Y.

Shelley (H. M.). **Report on a Case of Human Trypanosomiasis.**—*Nyasaland Protectorate Ann. Med. Rep. on the Health & Sanitary Condition for Year ending 31st December, 1928.* Appendix III. pp. 41–42.

Details are given of a case of trypanosomiasis in a European aged 32, who contracted the disease in Portuguese East Africa. The author states that the following were interesting features of the case :—

" 1. The dusky red macular rash on the anterior surface of the chest and abdomen, when first admitted to hospital.

" 2. The development of a bilateral orchitis, lasting one week. Another case of human trypanosomiasis in this country also developed a bilateral orchitis during treatment.

" 3. The occurrence of the typical circular erythematous rash 29 days after the commencement of treatment, and despite the fact that the patient had received 5·5 grammes of tryparsamide and 2 grammes of Bayer 205.

" 4. The apparent resistance of the parasites in the peripheral blood to tryparsamide and their rapid disappearance after one gramme of Bayer 205.

" 5. The haemoptysis of four ounces of blood, the patient having no signs of tuberculosis."

W. Y.

Sicé (A.). Alternance de l'infection sanguine chez quelques trypanosomés. [**Alternation of Blood Infection in Human Trypanosome Infections.**]—*Bull. Soc. Path. Exot.* 1929. Oct. 9. Vol. 22. No. 8. pp. 666–668. [Pasteur Inst., Brazzaville, French Equatorial Africa.]

The observations recorded in this paper were made on 12 patients, none of whom had received any previous form of treatment. It was decided to give them at Brazzaville a new biological treatment devised by one of the sleeping sickness doctors, the nature of which is not disclosed. The product used was found to have no trypanocidal power. Special attention is drawn to the alternate presence and absence of trypanosomes in the blood of the patients; the method of examination was always triple centrifugation.

Before treatment trypanosomes were found on gland puncture in 8 of the cases, but only two had the parasites in the blood. Twenty-four hours later trypanosomes were found in the blood of six cases. The results of seven examinations of the blood of 12 cases between the 3rd and 12th of August are shown in a table. It is seen that in only

two were trypanosomes found regularly in the blood; in nine cases they were sometimes present and sometimes absent. The remaining case in which trypanosomes were never found was rejected, as on August 8th *Sp. duttoni* were discovered in the blood.

Blanchard (1913) has already drawn attention to the spontaneous variations in the blood infection of four cases of sleeping sickness, and the present table confirms his observation. The author considers that these facts indicate the necessity of not limiting attention to the blood when attempting to make a diagnosis of trypanosomiasis, but of also performing gland puncture and lumbar puncture.

W. Y.

Maclean (George). **Notes on Treatment of Fifty-Two Cases of Rhodesian Trypanosomiasis with Bayer 205 and Tryparsamide.**—*Ann. Trop. Med. & Parasit.* 1929. Nov. 8. Vol. 23. No. 3. pp. 337–344. [1 ref.]

The author describes the results of treatment during an outbreak of human trypanosomiasis in the Ufipa District of Tanganyika Territory. The species of tsetse responsible was *G. morsitans*, and the acute nature of the disease, together with the finding of posterior nuclear forms in subinoculated rats, indicate that the disease was of the Rhodesian type. In all, 52 cases (diagnosed microscopically) were treated between November, 1924, and December, 1925. All the survivors were kept under observation until 1928.

The following are the conclusions:—

"Generally speaking, the earlier the treatment the better the chances of recovery. There is good reason to expect that an uncomplicated case taken in the first two or three weeks of infection will make a complete recovery, if given four grammes of Bayer 205 in three or four doses, the treatment being spread over a month. To allow a margin of safety it may be advisable to administer as much as eight grammes, but if this is done the urine should be watched daily for albumen. How far Bayer 205 should be withheld when albuminuria occurs is a matter for judgment in each individual case, but generally the treatment should cease until the albumen disappears if three grammes have already been given, but should not be withheld for more than ten or fourteen days if only two grammes or less have been given. An individual dose should not ordinarily exceed one and a half grammes. The optimum total dosage of Bayer 205 is not known, and a series of late cases on a prolonged course of treatment should be worth observing.

"Tryparsamide alone, though not generally regarded as satisfactory in this type of sleeping sickness, has given good results in some cases and would seem to deserve further trial. Solutions of this drug should always be made in distilled or freshly-collected rain water, and the solution should not be allowed to stand long or heated beyond blood heat. Should dimness of vision occur, treatment should cease until the sight is completely restored.

"Treatment by Bayer 205 followed by Tryparsamide gives better results than Bayer 205 alone. When the combined treatment is being given Bayer 205 should be administered in the same way as when the drug is given alone and after this course Tryparsamide should be given in 2 or 3-gramme doses at weekly intervals with or without a month's interval between the fourth and fifth, and the eighth and ninth injections, until at least 36 grammes are given. What interval should elapse between the last dose of Bayer 205 and the first dose of Tryparsamide is still a matter of conjecture, but a month has been found suitable.

"In the above series children generally reacted badly to treatment, but this may possibly be because the doses were too small. It has since been found that children tolerate both drugs extremely well.

"It is important that a series of treated cases who are in good health but whose cerebro-spinal fluid remains abnormal for several months after completing treatment, should be given a further course of tryparsamide without waiting for the development of any symptoms. These could then be compared in years to come with cases that had not been so treated.

"Work on the infectivity of Trypanosomes in relapsed cases is urgently needed."

W. Y.

Van den Branden (F.). Au sujet de l'arsénorésistance dans le traitement de la trypanosomiase humaine par le tryponarsyl. [**Arsenic Resistance in the Treatment of Human Trypanosomiasis by Tryponarsyl.**] —*Bull. Soc. Path. Exot.* 1929. July 10. Vol. 22. No. 7. pp. 540–542.

The work is a rejoinder to the paper of Barlovatz [see this *Bulletin*, Vol. 26, p. 708] dealing with arsenic resistance in the treatment of human trypanosomiasis with tryponarsyl [Belgian tryparsamide]. Experience has shown that for patients with normal spinal fluid a course of at least 30 gm. of tryparsamide is necessary. As regards patients with altered spinal fluid it is the condition of the fluid which should be the guide to treatment and criterion of cure of the patient. Barlovatz rarely records the state of the spinal fluid before treatment or at the periods of interruption of treatment, and the latter are usually untimely. There is likewise no record of the amount of albumin in the fluid and this is a matter of great importance.

The author has sometimes given up to 200 gm. of tryponarsyl without interruption in unfavourable cases, with amelioration of the general health and condition of the spinal fluid. Barlovatz has given quite inadequate doses with which it is possible to expect a cure. Patients insufficiently treated rapidly relapse and the method employed by Barlovatz with long interruptions undoubtedly favours the production of arsenic resistance.

W. Y.

Wilson (D. E.). **A Trial of Three Preparations made by the British Dyestuffs Corporation Ltd. in the Treatment of Trypanosomiasis in African Natives** (*T. rhodesiense*).—*Jl. Trop. Med. & Hyg.* 1929. Nov. 1. Vol. 32. No. 21. pp. 305–309. [1 ref.]

The three preparations referred to are (1) Fourneau 309, (2) Sample 2, and (3) Sample 3. They were received from the British Dyestuffs Corporation, Ltd., in order that their trypanocidal action in man might be tested. The tests were carried out in one of the sleeping sickness hospitals in Tanganyika Territory. The patients were unselected and had had no previous treatment. Three cases were treated with each drug and details are given.

The following are the conclusions :—

"Of the three substances tested Fourneau 309 (B.D.C.) was the only one which showed any trypanocidal action. As far as I am aware this is the first time that a British preparation of Fourneau 309 has been used in the treatment of human trypanosomiasis (*T. rhodesiensis*). Its action on the three cases in which it was employed was quite equal to that of Bayer 205 or the French preparation Fourneau 309.

" It seems rather extraordinary that two compounds so closely related, namely (B.D.C. Fourneau 309 and Sample 2 and 3) should show such marked differences in their trypanocidal action.

" Fairbrother and his colleagues (1925) found a similar difference in trypanocidal action between Fourneau 309 and some preparations of apparently closely allied chemical constitution in experiments on mice infected with *T. equiperdum*."

W. Y.

MACLEAN (George). **The Action of Präp. 3510 in Rhodesian Sleeping Sickness.**—*Ann. Trop. Med. & Parasit.* 1929. Nov. 8. Vol. 23. No. 3. pp. 345–348.

The drug in question was obtained from the firm of I. G. Farbenindustrie A.G., Hochst-am-Main, Germany. It is known as Präp. 3510, and is a white powder easily soluble in water. It is stated to be an arsenical compound, but the formula is not disclosed. The drug is made up in ampoules containing 1 to 2·5 gm. ; no information was given regarding doses.

Three cases were treated in April and May 1928 ; two were very advanced, but the third patient was comparatively robust. The result was not successful, as all the patients died. The author believes that death in the third case was probably accelerated by the drug. Details of the three cases are given. The first case received 3·75 gm. of the drug intravenously ; the second 2·5 gm. intramuscularly. The first two cases died on the 6th and 8th day, respectively, after treatment. The third case was given 2·25 gm. intramuscularly on the 1st day and 2 gm. on the 7th day ; he died on the 10th day.

As the observations made on these cases appear to suggest that the drug had a definite trypanocidal action, it was decided to continue the observations under modified conditions. A fourth case was accordingly selected and 1 gm. of Bayer was given to sterilize the blood. A week later 2 gm. of Präp. 3510 was given intravenously. There was little or no reaction and the patient was able to tolerate eight similar weekly injections without untoward symptoms and with very good clinical results. Nine months later he was, except for some pains in the legs, very well and was able to do heavy muscular work.

The conclusions are as follows :—

" The limits of the pharmacological dose of Präp. 3510 in man are not known, but there is reason to suspect that its action is much more toxic if there are large numbers of trypanosomes in the peripheral circulation when it is administered.

" It has proved much less efficacious than either Bayer 205 or Tryparsamide in moderate doses. While it may possibly be an efficient trypanosomicide in larger doses the margin of safety is so narrow that it is of no practical value when administered alone. Its action in association with Bayer 205 is being observed, but it will probably take some years before any definite conclusions can be arrived at about this method of treatment.

" The drug is well worth a trial in the various trypanosomiases of domestic stock."

W. Y.

COGHLAN (Bernard A.). **A Report on " BR. 68 " in the Treatment of Trypanosomiasis.**—*Trans. Roy. Soc. Trop. Med. & Hyg.* 1929. Aug. 26. Vol. 23. No. 2. pp. 197–199.

Two series of cases of Rhodesian sleeping sickness were treated with " BR.68." The first series consisted of six consecutive patients

arriving at the hospital (Tanganyika). Four of these had previously received treatment and two were fresh cases, both rather in an advanced stage. In the fresh cases three injections of 0·3 gm. and two of 0·6 gm. were given at weekly intervals. Two of the relapsed cases were similarly treated and two received four injections of 0·3 gm. and only one of 0·6 gm. The fresh cases were advanced; the blood was swarming with trypanosomes, and the cerebrospinal fluid was infected in both instances. The first injection produced a severe reaction, but the blood was still positive 24 hours later. On the second day the blood was negative, and continued so in one case for five days and in the other for twelve days. The subsequent injections caused the trypanosomes to disappear for a few days, but they invariably reappeared in the blood within a week, even when the dose was doubled. The relapsed cases seemed to improve at first, but the improvement was not maintained after the first two injections. The results were considered to be so bad that the drug was abandoned and the patients given a course of Bayer 205 and tryparsamide; their subsequent improvement was in marked contrast to their previous progress.

The second series of patients were also unselected, but they were all fresh infections. They were given 0·1 gm. of Bayer 205, followed by nine injections of BR.68 (six injections of 0·3 gm. and three injections of 0·6 gm.). Two patients died within two months of receiving the last BR.68 injection. Under the Bayer treatment they had considerably improved.

The general conclusion reached is that BR.68, although it has some action, cannot be considered to be a very useful addition to the list of trypanocidal drugs.

W. Y.

Van den Branden (F.). Essai de traitement de la trypanosomiase humaine chronique par le novatoxyl. [**Treatment of Chronic Human Trypanosomiasis by Novatoxyl.**]—*Bull. Soc. Path. Exot.* 1929. June 12. Vol. 22. No. 6. pp. 431–435. [Léopoldville Lab., Léopoldville.]

This paper describes the attempt to treat cases of human trypanosomiasis with a new German preparation, "Novatoxyl," i.e., the sodium salt of paraphenylglycinamido arsenic acid. The amount of drug available being very limited, it was decided to limit observations to four chronic cases.

Having no definite instructions regarding dosage, the author began with doses of 1 gm. and 1·5 gm. and subsequently found that he could give with impunity weekly doses of 2 gm. With a view to ascertaining the speed with which the peripheral blood was sterilized, six cases with trypanosomes in the blood were given a single intravenous injection of from 1 to 2 gm. of the drug; it was found that peripheral sterilization was produced by a dose of 2 gm. in approximately 10 hours.

Details are given regarding the treatment of the four chronic cases, all of which exhibited profoundly altered spinal fluid, with greatly increased lymphocytes and albumin. In one case the formula became normal after the patient had received 57·5 gm. of the drug; in two cases which received respectively 54 gm. and 53 gm. of the drug, the spinal fluid and general condition became very greatly improved; and in the fourth case, although there was a diminution in the lymphocytosis and quantity of albumin, the clinical condition did not improve.

None of the patients exhibited ocular trouble. The author concludes that although he cannot draw definite conclusions from four cases, there seems to be evidence that the drug has an action comparable to that of tryparsamide and tryponarsyl.

W. Y.

Launoy (Léon), Nicolle (Pierre) & Prieur (Marie). Détermination des doses liminaires préventives du composé 205-Bayer-309-Fourneau dans quelques trypanosomiases expérimentales. [**Determination of the Minimum Preventive Dose of Fourneau 309 in Experimental Trypanosomiasis.**]—*C.R. Soc. Biol.* 1929. June 28. Vol. 101. No. 22. pp. 650–653. With 1 graph in text. [1 ref.]

During the last year the authors have performed a large number of experiments with the object of ascertaining as exactly as possible the relationship between prophylactic doses of Fourneau 309 and the duration of the refractory period resulting. They have employed for this purpose mice, cats and guineapigs, and *Trypanosoma brucei, T. evansi* and *T. equiperdum.*

For the mouse the minimum preventive dose is defined as the smallest dose capable of protecting the animal for 30 to 40 days against one of the above-mentioned infections. In the cat the disease runs a slower course and it is necessary to modify this definition. For this animal the authors regard the minimum preventive dose as the smallest quantity of the drug which will protect the animal for about 60 days ; the duration of protection is determined by the number of days elapsing between the injection of the drug and the date of the last of a series of inoculations of the virus which failed to infect.

The results of experiments with mice are summarized in a table and a chart, and those performed on the cats are given separately in detail.

The following are the conclusions :—

1. In experimental trypanosomiasis of the mouse and cat the duration of the refractory period is proportional to the dose of the drug injected, at least in so far as the minimal and subminimal doses are concerned ; with larger doses this no longer appears to be exact.

2. Subminimal doses only produce a refractory period of short duration ; nevertheless, they may give rise to a peculiar condition of the animal which enables it to resist the infection for a long time and even to recover from it spontaneously. This is true both for mice and cats.

This result seems to indicate that the refractory state created by Fourneau 309 against experimental trypanosomiasis cannot be explained simply by the presence of the drug in the circulation or in the tissues.

W. Y.

Leupold (Frida). Die Verhütung einer Bayer 205-Festigkeit im simultanen Kombinationsversuch. [**The Prevention of Resistance to 'Bayer 205' in Simultaneous Combination Experiments.**]—*Arb. a.d. Staatsinst. f. Exp. Ther. u.d. Georg Speyer-Hause zu Frankfurt a.M.* 1928. No. 21. pp. 110–119. [1 ref.] [Georg Speyer House, Frankfurt a.M.]

The following are the conclusions :—

Trypanosomes experience, as the result of prolonged treatment with subtherapeutic doses of a trypanocidal substance, a change in their chemo-receptor apparatus, which expresses itself by the fact that they are no longer damaged by maximal doses of the drug ; they have in fact become drug-fast.

Arsenic, antimony and dye-fast strains are insensitive to 'Bayer 205'; and can in a short time, like a normal trypanosome strain, become fast to the drug.

Simultaneous treatment of trypanosomes with two chemically different trypanocidal substances (arsacetin and tryparosan, arsacetin and trypaflavin) accelerates in general the diminishing avidity taking place in the chemo-receptor apparatus, and leads to absolute resistance to both drugs.

On the contrary, there occurs in the combined treatment of 'Bayer 205' with arsacetin on the one hand, and with tryparosan or trypaflavin on the other, a hypersensitiveness of the trypanosomes to 'Bayer 205,' so that considerably reduced doses exert a sterilizing action.

In simultaneous combination experiments of 'Bayer 205' with arsacetin, tryparosan or trypaflavin, a pronounced retardation of the process of drug habituation can be seen.

W. Y.

Collier (W. A.) & Krause (Magdalene). Ueber die Wirkung eines unlöslichen Arsenpräparates auf die Trypanosomeninfektion der weissen Maus. [**The Action of an Insoluble Arsenic Preparation on a Trypanosome Infection in White Mice.**]—*Ztschr. f. Hyg. u. Infektionskr.* 1929. Oct. 12. Vol. 110. No. 3. pp. 516–521. [4 refs.] [Robert Koch Inst., Berlin.]

Experimental investigations have shown that certain substances insoluble in water have a pronounced action in certain diseases. It appeared of interest to ascertain whether insoluble arsenicals had any curative action. For this purpose the authors used an arsenical pyridin preparation 'BR 34 a' of Binz and Rath. This substance is closely related to 'BR 34.'

From the experimental work, which is set forth in detail, it appears that the insoluble 'BR 34 a' exerts a definite influence on mice infected with *T. brucei*. The drug had a prophylactic action if given not more than 2 days before inoculation of the trypanosomes. Similarly, subcutaneous injection of 1 cc. of a 1/2000 concentration in olive oil 30 minutes after the inoculation of trypanosomes prevented infection. The chemotherapeutic ratio was found to be 1 : 20. The action of the drug was equally favourable when given 24 hours after the inoculation of trypanosomes and at a time when parasites could actually be seen in the peripheral blood. Toxic doses of the drug injected into the muscles of rabbits gave rise to no inflammatory lesions.

W. Y.

Richet (Charles) & Gley (Pierre). Sur la toxicité de certains composés arsénicaux vis-à-vis du trypanosome *in vitro*. [**The Toxicity of Certain Arsenical Compounds for Trypanosomes in Vitro.**]—*C.R. Soc. Biol.* 1929. July 5. Vol. 101. No. 23. pp. 802–804.

The authors have attempted to measure the therapeutic activity of arsenical compounds by ascertaining in what dilution they are toxic to the trypanosomes *in vitro*.

The observations were made in Ringer-Locke solution with a pH of between 7·2 and 7·4. A solution of novarsenobenzol 1 : 10,000 is made in this fluid. A series of 11 haemolysis tubes is selected; into the 1st is put 10 drops of the 1 : 10,000 solution of novarsenobenzol, into the 2nd 9 drops and so on. Tube No. 2 receives one drop of Ringer-Locke, Tube No. 3, two drops and so forth. The eleventh tube contains 10 drops of Ringer-Locke and serves as the control. To each tube is then added 1 drop of the

blood of a mouse infected with *T. brucei*. A drop of the fluid is examined microscopically at frequent intervals to see whether the trypanosomes are living or dead. An arbitrary time limit of 30 minutes is fixed, and if the parasites are found to be living in one dilution at the end of this time the authors consider that they resist this dilution.

The results are given in a table. The pentavalent arsenicals studied had no action and '606' was not soluble in a liquid of pH 7·2 to 7·4.

In a later paper the authors propose to compare the results obtained by this method with those they have obtained *in vivo*.

[No mention is made of the temperature at which these *in vitro* experiments were conducted. Thirty minutes seem to be an absurdly short period on which to base conclusions: probably, however, it was enforced by the fact that the controls did not live much beyond this time. Nothing is said about the length of life of the controls.]

W. Y.

Roskin (Gr.) & Romanowa (K.). Arzneimittel und ultraviolette Strahlen. II. Mitteilung. Die kombinierte Wirkung von ultravioletten Strahlen und Novarsolan auf *Trypanosoma equiperdum*. [**Medicaments and Ultraviolet Rays. II. The Combined Action of Ultraviolet Rays and Novarsolan on** *T. equiperdum*.]—*Ztschr. f. Immunitätsf. u. Experim. Therap.* 1929. Vol. 62. No. 1/2. pp. 158–163. [3 refs.] [Microb. Research Inst., Education Commissariat R.S.F.S.R. Moscow.]

The following summary is given :—

1. The doses of novarsolan used, viz., 1 : 2000, 1 : 3000, and 1 : 4000 did not cure infection caused by the authors' strain of *T. equiperdum*.

2. The same doses of novarsolan, when followed immediately by an application of ultraviolet rays, produced complete sterilization of the mouse organism.

3. Smaller doses of novarsolan, e.g., 1 : 5000 and 1 : 6000, followed by ultraviolet rays were not, in most cases, followed by sterilization, but the relapse was definitely delayed.

W. Y.

Venturi (Luigi Carlo). Il naganol ed il moranyl nella cura della tripanosomiasi umana ed animale Ricerche sperimentali in vitro sopra un tripanosoma umano e tripanosomi animali. [**Naganol (Bayer 205) and Moranyl (Fourneau 309) in the Treatment of Trypanosomiasis. Experiments** *in vitro* **with One Human and Several Animal Trypanosomes.**]—*Arch. Ital. Sci. Med. Colon.* 1929. June 1. Vol. 10. No. 6. pp. 248–255. English summary p. 255. [Inst. of Trop. Path., Univ., Bologna.]

Blood was taken from the ears of guineapigs infected with *T. cruzi*, *T. marocanum*, *T. evansi*, *T. cameli*, *T. equinum* and *T. brucei* and placed in well-slides with dilutions of 1/10, 1/20, 1/50, and 1/100 of Bayer 205 and Moranyl respectively, and the effects watched for 1–3 hours. According to the action of the drug the parasites lost motility and collected round groups of corpuscles, and formed themselves into groups; occasionally only did they lie singly. The protoplasm then became granular, vacuolated, and the parasites disintegrated. The different species reacted differently, *T. brucei* proving the least resistant, *T. evansi* the most. No difference

was detected as regards the two drugs, which in fact are said to be chemically identical. [Tables are given, presumably to illustrate the results generalized in the letterpress ; they consist of figures, but unfortunately no reference can be found as to what the figures imply.]

H. Harold Scott.

HIRSCHFELDER (A. D.) & WRIGHT (H. N.). **Is Schnitzer's "Interference" between the Action of Two Chemotherapeutic Substances due to Surface Reactions?**—*Proc. Soc. Experim. Biol. & Med.* 1929. June. Vol. 26. No. 9. pp. 789–790. [2 refs.] [Pharmacol. Dept., Univ. of Minnesota, Rochester.]

BROWNING and GULBRANSEN discovered the remarkable fact that, although basic fuchsin cured rats infected with trypanosomes, and acriflavine had the same effect, if animals previously fed with basic fuchsin were infected with fuchsin-fast trypanosomes, and later acriflavine was injected, the therapeutic action of acriflavine was prevented and the animals died of trypanosomiasis. This action was referred to as the "Interference phenomenon." SCHNITZER confirmed these observations both with fuchsin-fast and with normal trypanosomes, and showed that it applied also to other triphenyl methane dyes, e.g., methyl violet and brilliant green, and to arsenicals, e.g., arsphenamine and arsacetin.

As these observations seem to raise fundamental questions in chemotherapy, it is of importance to determine whether they can be explained as merely surface reactions upon the trypanosomes or whether we must have recourse to more abstruse processes of metabolism or vital phenomena.

The authors investigated whether a similar interference could be demonstrated upon the growth and CO_2 production by yeast in the test tube. They found that yeasts which have been definitely stained with methyl violet or by brilliant green, in solutions too weak to affect the CO_2 production, are less sensitive to acriflavine than are normal yeast cells ; and vice versa yeasts stained similarly with acriflavine are less sensitive to methyl violet and brilliant green. The effect was not noticeable with basic fuchsin.

It is considered that these experiments represent a complete parallelism *in vitro* to Browning's and Schnitzer's 'interference phenomenon' *in vivo* and render it probable that the latter can be explained as a simple surface reaction.

W. Y.

BRUSSIN (A. M.). Zur Frage ueber das Phänomen der Interferenz. [**On the Interference Phenomenon.**]—*Ztschr. f. Immunitätsf. u. Experim. Therap.* 1929. Aug. 1. Vol. 62. No. 5/6. pp. 424–436. [13 refs.] [Microbiol. Research Inst., Education Commissariat R.S.F.S.R., Moscow.]

The following are the conclusions :—

1. The interference phenomenon, as described by BROWNING and GULBRANSEN, occurs not only in infections with *T. brucei* (Strain Prowazek), but also in infections with other trypanosomes.

2. Intensity of the interference phenomenon is, under optimum conditions of experiments, not equal ; it is determined by the trypanosome species and the individual properties of the macro-organism.

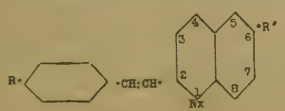
3. The interference phenomenon is in no way influenced by blocking of the reticulo-endothelial system.

W. Y.

Browning (C. H.), Cohen (J. B.), Ellingworth (S.) & Gulbransen (R.). **The Trypanocidal Action of Some Derivatives of Anil and Styryl Quinoline.**—*Proc. Roy. Soc.* 1929. July 4. Ser. B. Vol. 105. No. B735. pp. 99–111. [4 refs.] [Med. School, Leeds, & Path. Dept., Univ., & Western Infirmary, Glasgow.]

This paper deals with the trypanocidal action of an extensive series of anil- and styryl- quinolines, the bactericidal action of which has been recorded previously [*Proc. Roy. Soc.*, Ser. B, Vol. 100, p. 293 (1926); Vol. 103, p. 404 (1928)].

The anilquinolines have in general but little trypanocidal action, cure being effected by only one of those tried, viz., 2(p-dimethylamino-anil)-6-chloroacetyl-aminoquinoline methochloride and then only at the maximum tolerated dose. The styrylquinolines on the contrary are more effective, and also more toxic. Those tested may be represented by the following general formula :—



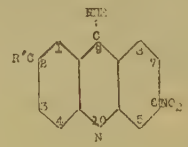
The conditions for effective trypanocidal action appear to be the simultaneous presence of an acylamino-group in either nucleus (i.e., at R or R_1) and of a primary (NH_2), or a tertiary (e.g., dimethylamino $N(CH_3)_2$) amino- group in the other, i.e., at R_1 or R. The nature of the quarternary group, X, is only important as affecting solubility. The two best trypanocides found were No. 8 [2(p-aminostyryl)-6-acetylamino-quinoline methochloride] which occasionally cured in doses of one fiftieth of the maximum tolerated, and No. 90 [2(p-acetylamino-styryl)-6-dimethylaminoquinoline metho-chloride] which appears to be equally good, with the exception that No. 8 also exerts some prophylactic action. No. 90 has but little trypanocidal action *in vitro*. Neither is absorbed from the alimentary tract. Resistance provoked by non-sterilizing doses of No. 90 was associated with high resistance to other trypanocides, except germanin and trypan-blue. The tests were carried out on mice infected with *T. brucei*, but Nos. 8 and 90 were also tried successfully in rabbits, Prowazek and ferox strains of *T. brucei* being used as in the tests with mice. No. 90 is rapidly removed from the circulation; thus, two minutes after an intravenous dose of 0·002 gramme per kilo to a rabbit, the substance cannot be detected in the blood. Urine from rabbits which have received No. 90 contains either the unchanged substance or an active derivative, since an alcoholic extract of the urine exhibits trypanocidal action.

T. A. Henry.

Schnitzer (R.) & Silberstein (W.). Ueber neue trypanocide Acridinfarbstoffe. Untersuchungen an homologen Reihen von 6-Nitro-9-Aminoacridinen. [**On New Trypanocidal Acridine Dyes. Investigations on Homologous Series of 6-Nitro-9-Aminoacridines.**]—*Ztschr. f. Hyg. u. Infektionskr.* 1929. Apr. 8. Vol. 109. No. 3 & 4. pp. 519–531. [6 refs.] [Robert Koch Inst., Berlin.]

The fact that acriflavin (3 : 6-diamino-10-methylacridinium chloride) introduced by Ehrlich and Benda as a trypanocide, has found

employment almost wholly as a bactericidal agent is typical of the way in which in recent years chemotherapeutical work on acridine derivatives has acquired a bactericidal rather than a trypanocidal objective. Among the numerous new acridine derivatives investigated by the authors only the 6-nitro-9-aminoacridines are dealt with in this paper, the principal interest of which lies in the demonstration of the effect of the nitro-group in position 6, in enhancing the trypanocidal action and of the further favourable effect brought about by the substitution of a doubly alkylated amino-group for a hydrogen atom in the amino-group in position 9. The formula shown below will serve as a general representation of the structure of the compounds dealt with.



In this formula the .NHR in position 9 is such a substituent as the dimethylaminooxypropylamino-group $.NH.CH_2.CHOH.CH_2.NMe_2$ whilst R_1 in position 2 is an alkyloxy group, such as methoxyl, (.OMe). The technique employed in the tests and the results obtained in a number of typical instances are tabulated in the original but as the object of the paper appears to be to direct attention to 6-nitro-9-aminoacridine as a basis for the synthesis of trypanocides, it will probably be sufficient to summarize the authors' conclusions as to the effect of various side-chains substituted in this nucleus, on the trypanocidal action. The doubly alkylated basic side chain (R) may either replace a hydrogen atom in the amino-group at position 9 or it may be directly attached to the carbon atom in position 1. Within a group of substances in which R has the same composition and position, modification of the trypanocidal action can be brought about in most cases by variation of R_1 (position 2) thus a 2-ethoxy-compound is usually less active than a 2-methoxy-compound and the latter less active than one in which there is no side-chain in position 2.

Toxicity and therapeutic effect do not always run on parallel lines. In some groups the most toxic members are also the most effective therapeutically, in others only the possibility of large dosage permits of the exhibition of any therapeutic effect. It is, however, possible by variation of the side-chains within the limits described above to achieve a favourable adjustment between the two. Thus the substance numbered 3043a, which has a glycyldiethylaminoethylamino group, probably $CH_2.NH_2.CO.CH_2.CH_2.NEt.CH_2.CH_2NH.$, in position 9 and an ethoxyl group $(.OC_2H_5)$ in position 2, has a therapeutic index 1/20 to 1/50 and is moreover one of the few instances in which ethoxyl is more effective than methoxyl in position 2. These substances are slow in action taking about 24 hours to sterilize the blood of a trypanosome-infected mouse. Trypanosomes which had become fast to acriflavin showed a definite, but diminished, susceptibility to some of the new compounds, indicating that resistance of this kind is probably confined to a portion of the molecule and is not to be regarded as resistance to acridine compounds in general.

T. A. Henry.

ARNAUD (R.). Technique nouvelle de dosage des albumines rachidiennes. [**New Technique for Estimation of Albumin in Cerebro-spinal Fluid.**]—*Bull. Soc. Path. Exot.* 1929. May 8. Vol. 22. No. 5. p. 337.

The determination of the albumin in cerebro-spinal fluid is such an everyday occurrence in sleeping sickness work that the discovery of a simple and rapid method is a matter of importance. The present method, which consists in the precipitation by hot trichloracetic acid, requires five hours to give the result.

The method recommended by the author consists in the precipitation of albumin at ordinary temperatures by the following reagents :—

Acetic acid	5·0 cc.
Carbon tetrachloride...	1·5 cc.
Alcohol, 95 per cent.	24·0 cc.

The mixture should be well shaken and preserved in a coloured and stoppered bottle. The technique consists in pouring 4 cc. of the cerebrospinal fluid into a Sicard's tube and adding at least 1 cc. of the reagent. At the zone of contact of the two fluids there is a milky precipitate ; the tube should then be stoppered and the two fluids well mixed. The results should be read after 20 minutes in the usual way.

It is claimed that the results are comparable with those yielded by the classical procedure, that the precipitate is even more regular and consequently the reading easier, and that it saves at least 4½ hours.

W. Y.

SICÉ (A.) & BOISSEAU (R.). Quelques résultats obtenus avec la technique nouvelle de dosage des albumines rachidiennes. [**Results obtained with the New Technique for the Estimation of Albumin in C.S.F.**]—*Bull. Soc. Path. Exot.* 1929. Oct. 9. Vol. 22. No. 8. pp. 679–681. [1 ref.] [Pasteur Inst., Brazzaville, French Equatorial Africa.]

The authors record the results of a comparison of ARNAUD's new method (above) of estimating the albumin in the spinal fluid with the old method. Their results, which are given in a table, show that Arnaud's method invariably gives distinctly lower values than does the classical method. In the case of normal spinal fluids and those containing but slight excess of albumin the differences, although marked, are not of great significance ; but as the quantity of albumin increases so do the differences in values obtained.

The conclusion reached is that Arnaud's new method does not constitute any advance and should not replace the classical method of employing hot trichloracetic acid for five hours. W. Y.

YORKE (Warrington), ADAMS (A. R. D.) & MURGATROYD (F.). **Studies in Chemotherapy. I. A Method for maintaining Pathogenic Trypanosomes Alive *in vitro* at 37° C. for 24 Hours.**—*Ann. Trop. Med. & Parasit.* 1929. Dec. 31. Vol. 23. No. 4. pp. 501–518. [8 refs.]

The following summary is given :—

" 1. As a preliminary step in an investigation of the mechanism of the action of drugs in experimental trypanosomiasis, it appeared desirable to study the action of the drugs in question *in vitro*.

" 2. For this purpose it was obviously necessary to discover some means whereby pathogenic trypanosomes could be preserved alive *in vitro*, in approximately undiminished numbers, at 37° C. over a period of at least 24 hours.

" 3. The efforts of previous investigators in this direction had not met with much success. It was, however, generally agreed that serum was the best medium, and that it was much easier to keep the parasites alive at laboratory temperature than at 37° C. It is not possible to obtain from this work information having any pretence to quantitative value, and so far as work at the body temperature is concerned, the only statement we have been able to discover of any real value is that of Rothermundt and Dale (1912), who merely recorded that in guinea-pig serum they were able to keep trypanosomes alive for at least 5 hours; the important question whether the number of parasites decreased substantially during this period, or whether the parasites were present in the same number at the end of the period as at the beginning is ignored.

" 4. Our own experimental work showed that it is possible to maintain a trypanosome suspension alive *in vitro* at 37° C., without any appreciable diminution in the number of individuals, during at least the first 24 hours.

" 5. The method of preparing such suspensions and of observing changes in the number of parasites occurring in them, from time to time, is described.

" 6. It is shown that serum—fresh, or deactivated at 56° C. for half an hour—from the rabbit, ox, sheep, horse or pig, are about equally efficacious as supporting media, and that physiological saline, Ringer's solution—with or without the addition of glucose—nutrient broth and broth containing 0·2 per cent. glucose are comparatively useless.

" 7. Normal human serum, even in high dilutions, was found rapidly to destroy *T. rhodesiense* and *T. equiperdum* at 37° C. *in vitro*: it had, however, no trypanocidal action on *T. gambiense*.

" 8. It was further shown that the concentration of trypanosomes in the medium is a matter of vital importance. The parasites live longest provided their concentration does not exceed about 1,000 per cmm.; if they are present in concentrations grossly exceeding this number, they die rapidly. The explanation of this fact is, doubtless, bound up with the great metabolic activity of the trypanosomes which, when the parasites are present in considerable concentration, rapidly deprives the medium o its nutrient properties and particularly of its glucose.

" 9. The presence of glucose is essential for the life of trypanosomes *in vitro*. Information is supplied concerning the relatively enormous quantity of glucose consumed by these parasites. It was found that 0·25 cc. of heavily-infected mouse blood, containing approximately 400 million parasites, sufficed, when suspended in 5 cc. of sheep serum, to which glucose had been added, to cause within 1 hour the disappearance of between 2 mgm. and 2·5 mgm. of sugar, and within 5 hours of between 12 mgm. and 12·5 mgm."

B. Blacklock.

Rosenthal (F.). Weitere Untersuchungen ueber den trypanoziden Heilmechanismus des menschlichen Serums. VI. Mitteilung. Verteilung, Umwandlung und Untergang der trypanozidogenen Substanzen des meschlichen Serums im Tierkörper. [**Further Investigations on the Trypanocidal Curative Mechanism of Human Serum. VI. Distribution, Transformation and Destruction of the Trypanocidogenous Substances of Human Serum in the Animal Body.**]—*Ztschr. f. Immunitätsf. u. Experim. Therap.* 1929. Aug. 1. Vol. 62. No. 5/6. pp. 464–492. [36 refs.] [Med. Clinic, Univ., Breslau.]

After referring to the numerous papers which indicate that the trypanocidal power of human serum is in some manner associated with

a function of the liver, Rosenthal points out that the question of the mechanism of the curative action of human serum in experimental trypanosome infections is still little understood. Since human serum has no lethal or harmful effect on trypanosomes in the test tube some biological mechanism must occur in the body of the treated animal whereby the substances present in human serum are converted into the lethal substances. In fact, we have here a parallel to the indirect action of certain chemotherapeutic substances, e.g., the pentavalent arsenicals which likewise are inactive *in vitro*, and only disclose their curative properties in the animal body. In previous papers [this *Bulletin*, Vol. 19, p. 154 and p. 520, Vol. 20, p. 337 and p. 700, Vol. 22, p. 143 and p. 537] the author and his collaborators have shown that the reticulo-endothelial system of the injected animal plays an essential part in the curative mechanism of human serum.

The present work was undertaken with the object of ascertaining what changes took place in human serum in the animal body. He set himself the task of following the destiny of human serum in its course through the animal body, for which purpose the demonstration of trypanocidal substances in obtained animal material served as a biologically distinctive sign.

The following are the conclusions :—

1. The trypanocidal action of human serum is apparent only after injection into animals.

2. Analysis shows that in the animal body a conversion of the preformed inactive substance in the human serum into the real curative body is necessary ; this is first produced as an intravital conversion product from the human serum circulating in the animal body. The initial substance and the conversion product are designated respectively as trypanocidogenous and trypanocidal bodies. The proof of the trypanocidogenous initial substance in the animal depends on the same properties which are characteristic of human serum, viz., complete inactivity *in vitro*, failure to combine with the parasites in the test tube, and pronounced trypanocidal power when introduced into the animal. For proof of the intravitally formed trypanocidal substance its combination with trypanosomes in the test tube is required.

3. After injection of human serum the blood of the treated animal acquires pronounced curative properties which, fundamentally, is dependent on the conversion in the circulation of the preformed initial substance of human serum. It can accumulate here in concentration which considerably exceeds the concentration existing in human serum. This indicates that, on the introduction of the human serum into the treated animal, there occurs an intravital isolation of the active principle.

4. The plasma alone is to be considered as bearer of the therapeutic products of the blood of animals treated with human serum.

5. Spread of the trypanocidal substances into the organs is not found to any appreciable extent. Likewise cell suspensions from organs are free from trypanocidal substance, so that absorptive binding does not occur.

6. Excretion of the trypanocidogenous serum substances in the urine does not occur. The disappearance of these substances must result from their being worked up further in the metabolism of the animal organism.

7. According to their biological behaviour in the animal body the trypanocidogenous substances of human serum are characterized as follows : by their relatively slow transformation in the organism, by their long sojourn and their pronounced accumulation in the blood stream, by their slight escape into the tissues and by their failure to be excreted in the urine. Their distribution and their destiny in the organism obey other laws than do, for example, bacterial toxins (Bieling and Gottschalk).

8. The intravitally formed trypanocidal transformation products of human serum evade recognition as a rule in the conditions of *in vitro* experiments. Their presence can, however, sometimes be disclosed by binding experiments. The trypanocidal substances must exhibit intermediate products which on their formation are taken up by the trypanosomes, the intermediate steps being passed very quickly. The reticulo-endothelial cell system takes a part in the curative mechanism of human serum.

9. Through inquiry of the amount and consumption of the trypanocidogenous substances a balance of the trypanocidal curative mechanism of human serum can be made.

W. Y.

ROSENTHAL (F). Ueber Störungen der trypanociden Serumstruktur bei der perniziösen Anämie. [**Fluctuations of the Trypanocidal Substance in Serum in Pernicious Anaemia.**]—*Klin. Woch.* 1929. July 30. Vol. 8. No. 31. pp. 1436–1437. [16 refs.] [Med. Clinic, Univ., Breslau.]

After discussing previous literature relating to this and allied subjects, the author passes to a consideration of his own observations on the trypanocidal power of the serum of ten cases of pernicious anaemia. The serum was obtained at various stages of the disease. In order to determine quantitatively the trypanocidal titre, the author had recourse to his previous technique, viz., the simultaneous intraperitoneal infection and subcutaneous injection of decreasing amounts of serum in 20 gm. mice.

The results obtained with the serum of the ten cases of pernicious anaemia are given in a table from which it is seen that in three cases there was no decrease in the trypanocidal titre, that in three cases there was definite decrease, and that in four cases there was pronounced decrease. There was apparently no correlation between the degree of anaemia and the trypanocidal titre. In those cases in which there was pronounced decrease of trypanocidal titre and in which a complete remission occurred there was a recovery of the trypanocidal titre to normal.

W. Y.

KLIGLER (I. J.). **Susceptibility and Resistance to Trypanosome Infection. VI. The Course of the Infection in Splenectomized Rats.**—*Ann. Trop. Med. & Parasit.* 1929. Nov. 8. Vol. 23. No. 3. pp. 315–324. With 2 charts. [7 refs.] [Hyg. Dept., Hebrew Univ., Jerusalem.]

In a preceding paper [this *Bulletin*, Vol. 26, p. 715] it was pointed out that the rat offered a type of resistance similar in kind but different in degree from that observed in a guineapig. It was considered that this resistance was probably referable to the reticulo-endothelial system, and consequently it seemed to be of interest to observe the course of infection in splenectomized rats. The fact that splenectomized rats developed an acute Bartonella infection, and succumbed in five or six days before the trypanosome infection had run its course, presented a serious difficulty. This difficulty was eventually eliminated by administering salvarsan prior to the removal of the spleen. As shown by MEYER, this procedure prevented the appearance of Bartonella for some time.

The following are the author's conclusions :—

" 1. Salvarsan increases the resistance of normal rats to a trypanosome infection and appears to exert a protective effect on the red blood cells. The former effect is either absent or greatly reduced in splenectomized rats.

" 2. Splenectomized rats treated with neosalvarsan to prevent a Bartonella infection show a complete absence of resistance to a trypanosome infection when the inoculation is given intraperitoneally. The course of infection in such rats follows a simple curve of geometric progression.

" 3. No corresponding reduction in resistance is noted in such rats when the inoculation is given subcutaneously. This is apparently attributable to the action of the salvarsan.

" 4. In normal rats the course of the infection is more rapid if the inoculum is given subcutaneously than it is when given intraperitoneally."

W. Y.

KLIGLER (I. J.), GEIGER (A.) & COMAROFF (R.). **Susceptibility and Resistance to Trypanosome Infections. VII. Cause of Injury and Death in Trypanosome Infected Rats.**—*Ann. Trop. Med. & Parasit.* 1929. Nov. 8. Vol. 23. No. 3. pp. 325–335. [14 refs.] [Hyg. Dept., Hebrew Univ., Jerusalem.]

The cause of death in experimental trypanosome infections has been the subject of considerable discussion. Two opposing views have been evolved to explain the cause of death in rats. SCHILLING and others assume that death is due to a toxic substance liberated by the disintegration of the parasites, whilst, on the other hand, SCHERN and his supporters believe that the cause of death is to be found in the exhaustion of the blood sugar and glycogen reserve. The authors believe that neither view is supported by experimental facts. One aspect of the problem seems to have escaped the notice of previous workers. Although there is general agreement that the blood sugar concentration is depressed, no attention has been given to the possible harmful effect of intermediate products of sugar metabolism.

With a view to investigating this question, the authors decided to determine the lactic acid concentration and alkali reserve in the blood at various stages of the infection. They reached the following conclusions :—

" 1. Injection of large doses of trypanosomes, or serum taken when the trypanosome number is at its maximum, does not produce any visible toxic symptoms in rats.

" 2. Daily injection of glucose to supplement the food affects the course of infection favourably only if started at the time of inoculation and not if started after the incubation period.

" 3. The oxygen consumption of trypanosome infected rats is not increased ; towards the end of the infection it appears somewhat lower than normal.

" 4. Parallel with the increase in the number of trypanosomes, there is a progressive increase in the concentration of lactic acid in the blood—in the later stages up to three or four times the normal.

" 5. It is suggested that the pathological processes are engendered by the metabolism of the trypanosomes which results in the rapid production of lactic acid, leading to exhaustion of the alkali reserve and probably also to a depression of the oxidative processes by the specific effect of lactic acid on the haemoglobin.

" 6. Experiments are under way which indicate that injection of bicarbonate tends to increase the life of the animals as compared with the untreated controls."

W. Y.

Scheff (Georg). Ueber den intermediären Stoffwechsel der mit Trypanosomen infizierten Ratten. [**The Intermediate Metabolism of Rats infected with Trypanosomes.**]—*Biochem. Ztschr.* 1928. Sept. Vol. 200. pp. 309–330. With 2 text figs. [Refs. in footnotes.] [Hyg. Inst., Elisabeth Univ., Pécs.]

In this paper, which is of a biochemical nature, the author has investigated the changes in the carbohydrate, protein, and fat metabolism in rats experimentally infected with trypanosomes. Observations are also made on the changes in the red cell count, on the oxygen waste, and on the acid-base equilibrium.

Considerations of the results obtained indicate that the trypanosomes, as blood parasites, primarily deprive the organism of carbohydrates and of oxygen, and eventually also of other substances. So long as the fresh supply of the former is effective and can meet the demand there is no noticeable disturbance. So soon, however, as the liver suffers a secondary damage from functional over-work a state of hypoglycaemia arises. The simultaneous, although less pronounced, disturbance of protein metabolism is likewise the result of a direct action by the trypanosomes and of a secondary loss of function of the liver.

With the increase of trypanosomes in the blood the destruction of red cells becomes ever greater. The consumption of oxygen by the trypanosomes and the anaemia is restored so far as the oxygen supply permits. There develops, however, towards the end of the infection a hitherto undescribed form of internal asphyxia, which is very ominous for the liver of the rat. The disturbance of metabolism and the asphyxia are followed by acidosis, which, as is known, contributes to the decline of the reaction capacity of the host.

Irreversible changes in the regulation system of the animal gradually occur; these lead to the death of the rat. The fact that the morphological picture bears no relationship to the severity of the process does not invalidate this statement, because the changes occur with such great rapidity. There is no doubt that the intensity of the disturbance is directly proportional to the number of trypanosomes: and it is probable that a certain number of trypanosomes is necessary to produce the changes observed in the animal host. This interpretation is naturally only correct if the toxic action is left out of account, a procedure for which we have every ground.

Whether in chronic infections of other animals (e.g., guineapigs) with periodic appearance and disappearance of parasites similar processes occur is a matter which requires investigation. The part played by the internal secretion glands and by the reticulo-endothelial cells must also be taken into consideration. W. Y.

Zotta (G.) & Radacovici (E.). Contribution à l'étude du métabolisme du glucose sanguin dans la trypanosomiase expérimentale. [**Metabolism of Blood Glucose in Experimental Trypanosomiasis.**]—*Arch. Roumaines Path. Expérim. et Microbiol.* Paris. 1929. Mar. Vol. 2. No. 1. pp. 55–80. With 7 charts. [26 refs.] [Serolog. Inst., Bucharest.]

—— & ——. Sur les variations de la glycémie dans la trypanosomiase. —*C.R. Soc. Biol.* 1929. Oct. 18. Vol. 102. No. 26. pp. 129–130. [2 refs.]

The authors briefly review the work of Schern and others on this subject. In their own experiments they used guineapigs infected with *T. brucei* (strain Mesnil).

For the sugar estimations they employed the method of Bang, since this requires only small quantities of blood and thus allows of daily examinations. The examinations were always made between 4 and 5 p.m., i.e., eight hours after the last meal. The diet was normal.

The following are the conclusions :—

1. In guineapigs infected with nagana a progressive hypoglycaemia, proportional to the increasing number of trypanosomes in the blood, was not observed.
2. The variations of the degree of glycaemia were irregular, sometimes above and sometimes below the normal, suggestive of a disorder of the sugar-regulating centre, but in no case of a direct utilization of the blood glucose by the trypanosomes.
3. On the contrary, the constant phenomenon in the evolution of trypanosomiasis is a pre-mortal hypoglycaemia.
4. This appears quite suddenly without any previous progressive diminution in the blood sugar ; in fact, it is more often preceded by a phase of hyperglycaemia.
5. The terminal hypoglycaemia is perhaps due to a nervous mechanism set in motion by the direct action of the trypanotoxin on the sugar-regulation centre or by an indirect action through the suprarenal capsules.
6. Moreover, terminal hypoglycaemia is not specific for trypanosomiasis. It is a biological state characterizing the premortal period of a large number of diseases.

W. Y.

Angolotti (Enrique) & Carda (Pedro). La glucemia en la tripanosomiasis experimental del cobaya. Nota preliminar. [**Glycaemia in Experimental Trypanosomiasis of the Guineapig.**]—*Medicina Países Cálidos.* Madrid. 1929. Sept. Vol. 2. No.5. pp. 431–435. With 1 text fig. [9 refs.] French summary p. 435. [Parasit. Lab., Faculty of Med., & Red Cross Dispensary, Madrid.]

Usng the method of Hagedorn-Jensen, the authors determined the degree of glycaemia in the blood of guineapigs infected with *T. brucei*. They found an increase of the blood sugar proportional to the intensity of the infection : in two cases the glycaemia increased progressively, and only decreased shortly before death.

W. Y.

Locatelli (Piera). Les mégacaryocytes des cobayes trypanosomés. [**The Megacaryocytes of Trypanosome-Infected Guineapigs.**]—*C.R. Soc. Biol.* 1929. Aug. 13. Vol. 101. No. 25. pp. 1048–1050.

The author discusses the changes in the system of megacaryocytes found in guineapigs which have died from an infection with *T. equiperdum* or *T. brucei*. The nucleus particularly is profoundly changed ; the cytoplasm may be either basophil or oxyphil. Those showing nuclear changes have almost always a basophil cytoplasm : the degeneration of the nucleus precedes the degeneration of the cytoplasm (vacuolation, etc.). The reaction is the more intense the longer the period the animal has survived : in animals which lived for 3 to 4 months after inoculation one finds nuclei in all stages of pycnosis. On the contrary, if the animals died shortly after infection the most striking feature is the remarkable frequency of nuclear mitosis. The fact that in the animals which exhibit considerable nuclear mitosis one also encounters cells with pycnotic nuclei and also quite young forms, megacaryoblasts in all stages of differentiation, leads one to suppose that the pathogenic stimulus which causes degeneration of

the adult megacaryocytes accelerates the development of the young forms. In infections of longer standing the young forms are more rare, owing to the depletion of the reserves of the organism.

W. Y.

LEVINSON (L. B.). Der Einfluss von Alkohol auf die Infektion mit *Trypanosoma gambiense* bei weissen Mäusen. [**The Influence of Alcohol on** *T. gambiense* **Infection in White Mice.**]—*Zent. f. Bakt.* I. Abt. Orig. 1929. Nov. 30. Vol. 114. No. 7/8. pp. 488–492. With 4 graphs in text. [1 ref.] [Microbiol. Research Inst., Education Commissariat R.S.F.S.R., Moscow.]

Mice infected with the author's strain of *T. gambiense* ran a course lasting about 3 weeks. In order to control exactly the amount of alcohol administered, it was given *per os* by the method described by ROSENHOLZ (1926). Each mouse was given 0·3 cc. of 15 per cent. alcohol, which is approximately 2·2 cc. of absolute alcohol per kilo. of body weight, assuming the average weight of the mouse to be 20 gm. This dose was well tolerated, only an insignificant proportion of the animals dying, and then only when the alcohol had been given for many days. Some mice were limp after the dose and lay motionless for many hours, but recovered completely.

The results of the experiments, which are set forth in charts and tables, showed that the administration of this dose of alcohol, beginning the day before infection and either daily or every other day throughout the disease, exerted no influence upon the course of the infection. The daily administration of the alcohol 7 to 14 days before infection and afterwards until the time of death hastened the end quite perceptibly. In mice which had been poisoned for a sufficiently long time the infection ran a more severe course than in the control animals.

W. Y.

v. RAZGHA (Andreas). Ueber die Zuchtung der menschenpathogenen Trypanosomen. [**On the Cultivation of Trypanosomes Pathogenic to Man.**]—*Ztschr. f. Parasitenk.* 1929. June 17. Vol. 2. No. 1. pp. 55–66. With 1 text fig. [15 refs.] [Inst. for Ship & Trop. Diseases, Hamburg.]

A brief summary of the efforts of previous workers in this direction is given. In his first experiments Razgha employed Ponselle's (1924) hypotonic medium. This consists of equal parts of rabbit serum (for subcultures defibrinated rabbit blood) and of the following solution: Varying amounts of NaCl, from ·3 to ·8 gm., according to the trypanosome species, to 100 cc. of double distilled water: to this is added Witte's peptone 2 gm. and gelatine 2 gm. and finally 1 cc. of normal Na_2CO_3 solution. According to PONSELLE this medium has two peculiar properties, firstly, its hypotonic character, and secondly, its capacity, through adsorption, of rendering inactive the antiparasitic immune body of the inoculated infected blood. It is recommended that only pure gelatin—Coignet or Medaille d'Or—should be used, and that it should be thoroughly washed daily for six days in distilled water, and finally hardened in 95 per cent. alcohol. The gelatin and peptone should be dissolved at 100° C.; the medium is sterilized in the autoclave at 110° C. and can be kept at room temperature for several days. The peculiar physico-chemical character of this medium is shown by the fact that when blood is added the corpuscles sink to the bottom with remarkable speed.

As the patient himself had very few parasites (*T. gambiense*) in the blood, a monkey, *Macacus rhesus*, was inoculated; and as soon as its blood showed 2 or 3 trypanosomes to an oil immersion field, 1 to 3 drops were inoculated into the culture tubes containing Ponselle's medium. The tubes were left two weeks in a dark place and then examined, but no trypanosomes were found.

As the medium in these tubes was found to exhibit a fine fibrin network, and even at times a distinct blood clot, it was decided not to inoculate the citrated blood directly into the tubes, but first to dilute it with Ringer's solution and then, after centrifugation, to inoculate the clear supernatant fluid containing the trypanosomes. Notwithstanding this improved technique the cultures were still negative. To his surprise, however, the tube containing the remainder of the supernatant fluid and deposit, which had been kept with the culture tubes as a sort of control, was found to contain large numbers of parasites. This simple medium, therefore, appeared to be an excellent culture medium for *T. gambiense*.

Further work showed that the serum of only man and monkey would serve; that of other laboratory animals, e.g., rabbit, rat, and goat, failed. In his experiments the author therefore practically limited himself to human blood. His medium consisted of equal parts of sterile Ringer's solution (with ·6 per cent. NaCl) and of citrate human blood. The blood was obtained from a vein of the arm into a sterile syringe containing ¼ vol. of 2 per cent. sodium citrate in ·85 per cent. NaCl solution. The medium was then divided amongst tubes containing 2 to 3 cc. Inactivation is unnecessary, but it is preferable to allow the medium to stand for several days before inoculating it.

Successful cultures of the recently isolated *T. gambiense* strain were obtained in 31 of 40 attempts. In one observation living flagellates were found as long as the 44th day and in another up to the 40th day. The inoculated tubes were kept at room temperature, preferably at 22–24° C.; at higher temperatures the trypanosomes had a detrimental action on the parasites. In his work with *T. gambiense* the author did not notice any pronounced difference resulting from variations in the salt concentration, but he has the impression that ·6 per cent. NaCl gives the best results.

During the first two days, the trypanosomes decrease greatly in number and many degeneration forms are seen. A certain number of individuals, however, survive and divisional forms are to be seen. The appearance of cultural forms is first manifest on the 3rd or 4th day; these exhibit much greater translatory movement than do the blood forms. In stained preparations the general size of the cultural forms is found to resemble that of the blood forms, but the posterior end is more pointed and the blepharoplast moves forwards to occupy a position intermediate between that of the nucleus and the posterior extremity; the undulating membrane is narrowed and the protoplasm contains small granules or vacuoles. During the succeeding days the blood forms become scantier and the cultural forms more numerous. Between the 3rd and 6th days rosettes can be seen for the first time.

After a time—usually at the end of the first week—almost without exception a highly refractile granule appears at the junction of the middle and posterior thirds of the trypanosome body. This, which is a striking feature in fresh preparations, but cannot be seen in Giemsa and stained preparations, is probably nothing else than the blepharoplast vacuole. The further development of the trypanosomes is always in the direction of slender forms, and at the same time the body becomes more and more stuffed with granules which stain deep blue to black. Typical crithidia have not yet been seen, but the extremely long and narrow form exhibits a striking resemblance to the forms found in the gut of Glossina.

Subcultures made during the period of active multiplication of the parasites are successful and behave as the parent culture. Attempts to subculture further were not successful.

During his investigations a second strain of *T. gambiense* was isolated from a patient in hospital. This allowed the author to compare the behaviour of this strain with that of the earlier strain and of certain old strains which had been long maintained in the laboratory by animal passage. For this purpose he used a strain of *T. gambiense* kept for 8 years in rats and two strains of *T. rhodesiense* kept in animals for 5 and 17 years,

respectively. Seven attempts to culture the older *T. rhodesiense* strain failed, and only the twelfth attempt was successful in the case of the other *T. rhodesiense* strain, and the fifth in the case of the old *T. gambiense* strain. On the contrary, cultures with the new *T. gambiense* strain were always successful, and the cultures lived longer than those made from the older strain.

The author believes the failure of previous attempts to culture *T. gambiense* may be partly explicable by the fact that the attempts were made with old strains. Possibly, the failure with old strains was due to the gradual development of a susceptibility to human serum, or possibly to the fact that prolonged sojourn in the vertebrate host had so changed the parasite that it was no longer capable of developing in the vertebrate host or in the culture tube.

That a susceptibility to human serum can be produced as the result of prolonged passage through laboratory animals is known from the work of Mesnil, Zeiss and others. According to Mesnil, serum loses its power to damage trypanosomes if it is kept for several days (Zeiss's observations do not support this), and consequently it is desirable to keep the medium, when it has not been deactivated, for several days before use. Whilst the susceptibility to human serum first appears after prolonged passage through animals, and even then not always, the work of Duke has shown that animal passage for two years or even less destroys the capacity of trypanosomes to develop completely in Glossina. For these reasons the author favours the latter alternative as the explanation of his non-success in attempts to culture old strains.

In conclusion, the author refers to observations made regarding the capacity of his cultures to infect mice. Up to six days the results of culture inoculation did not differ appreciably from those of blood inoculation. From the seventh day onwards the cultures had apparently lost their power to infect mice. The author, however, refers to the low pathogenicity of his strains of *T. gambiense* for mice, and states that more work remains to be done on this subject.

W. Y.

i. Galliard (Henri). Remarques sur la culture de *Trypanosoma cruzi* Chagas. [**Notes on the Cultivation of** *T. cruzi*.]—*Ann. Parasit. Humaine et Comparée.* 1929. Sept. 1. Vol. 7. No. 5. pp. 367–376. With 3 text figs. [29 refs.]

ii. ——. Envahissement précoce et intense de la cavité abdominale chez la souris au cours des infections à *Trypanosoma cruzi*. [**Early Invasion of Abdominal Cavity in Mice infected with** *T. cruzi*.]—*Ibid.* pp. 377–380. [2 refs.] [Parasit. Lab., Faculty of Med., Paris.]

i. The author has been able to isolate in pure culture four different strains of *T. cruzi*, two from Brazil, one from Uruguay, and one from Paraguay. From the point of view of culture, all behaved in a similar fashion. Abundant cultures of great longevity (six months) were obtained in each case. A semi-solid medium of the type described by Wenyon was used and to this was added sugar and whole ox blood. The constitution of the medium and the amount of chlorides was found to be of importance for a rapid and intense development of the parasites. The following formula was used :—

Water	1,000 cc.
Gelatine	4 gm.
Glucose	2 gm.
Sodium chloride	4 gm.

Under such conditions at ordinary temperatures the culture developed rapidly. The temperature was not found to have much action provided

it did not exceed 25° C. The evolution of the cultural forms varied according to the medium. In the semi-solid medium used by the author crithidial forms sown in the course of subculture divided actively but never became converted into leishmania or leptomonas forms and never gave rise to rosettes, such as are seen in liquid media. In recent cultures (15 days to two months) the trypanosomes exhibited a remarkably uniform morphology, but in older cultures polymorphism was the rule. When hypotonic media (medium of Ponselle) were used, the cultures developed rapidly at ordinary temperature, and in them it was possible to observe very clearly the different stages of the evolution of the metacyclic trypanosomes and of degeneration forms. It appeared that the hypotonicity rather than the temperature exhibited a favourable action on the production of trypanosome forms.

ii. In the course of experiments on the inoculation of cultures of *T. cruzi* the author observed some interesting facts bearing on the evolution of the infection in the rat and mouse. The virus used was obtained from naturally infected *Triatoma rubrovaria* captured near Montevideo. The cultures inoculated were those of the 11th passage. An endeavour was made to trace the evolution of the inoculated forms in the peritoneum, but at the end of one dozen hours nothing was found. The peritoneal cavity, however, at the end of 48 hours revealed the presence of trypanosome forms, which, although scanty at this time, rapidly increased in number. The parasites found were typical blood forms and quite different from the metacyclic trypanosomes of the culture.

In order to investigate the matter further, rats and mice were inoculated with a culture under the skin of the back, and at the end of 48 hours the author was able to discover the commencement of a peritoneal infection which developed in an entirely similar manner. Consequently, the site of inoculation had nothing to do with the localization of the infection, which is apparently due to a tropism.

The evolution of the infection is variable. In the rat it is not very marked and disappears after some days. In the mouse the infection persists throughout the disease. The evolution is progressive, and after some days may reach an extraordinary intensity, even before the parasites have appeared in the peripheral blood, and in such cases death may supervene without apparent infection. Numerous developmental forms are found in the abdominal muscles (leishmania) and in the serous cavities (leishmania and leptomonas).

W. Y.

i. Torres (C. Magarinos) & de Azevedo (A. Penna). Cellules géantes kystiques chez l'armadille (*Dasypus novemcinctus* L.), qui présente l'infection spontanée par le *Trypanosoma cruzi* Chagas, 1909. [**Cystic Giant Cells in the Armadillo presenting Spontaneous Infection by** *T. cruzi*.]—*C.R. Soc. Biol.* 1929. Nov. 4. Vol. 102. No. 28. pp. 412–414. With 2 text figs. [1 ref.]

ii. —— & ——. Cellules géantes kystiques chez le chien infecté expérimentalement par *Trypanosoma cruzi*, souche de l'armadille. —*Ibid.* pp. 416–418. With 2 text figs. [Oswaldo Cruz Inst., Rio de Janeiro.]

i. Whilst examining the tissues of an armadillo captured in the state of Minas Geraes, Brazil, which at the time it was killed

contained numerous *T. cruzi* in the peripheral blood, the authors found scanty Leishmania forms in the myocardium. A most interesting discovery, however, was the presence of large agglomerations of *T. cruzi*, not in the muscle fibres, but in the cytoplasm of giant cells. The infected cells were covered with a very distinct membrane constituting a true cyst wall of double contour; within the double wall is a clear space apparently without structure. The cells were of large size varying from $20 \times 15 \mu$ to $40 \times 30 \mu$. In the authors' opinion what CROWELL (1928) describes as "the presence of a parasitic thrombus in a small artery in the myocardium" is probably a gigantic cyst comparable to that found by them.

ii. In the second note the authors state that they have found similar cysts in the heart, thyroid and kidneys of dogs experimentally infected with *T. cruzi* from the armadillo. Further details regarding the structure of the cyst are given.

W. Y.

CAMPOS (Ernesto de Souza). Trypanosomiase americana congenita experimental. [**Congenital American Trypanosomiasis Experimentally Transmitted.**]—*Bol. Biol.* S. Paulo. 1929. June 30. No. 15. pp. 28–33. With 6 figs. [3 refs.] [Microbiol. Lab., Faculty of Med., S. Paulo.]

A bitch was infected at the age of 9 months with *T. cruzi*; after a time the parasites were no longer found in the peripheral blood, but at two subsequent pregnancies, one six months and the other nineteen months later, the infection was found to have been transmitted to the puppies. Some of these were killed and the pathological histology characteristic of the disease was confirmed in the various tissues. Moreover, the blood from one of these reproduced the disease when inoculated into a healthy animal.

H. Harold Scott.

ADANT (Max). Contribution à l'étude de l'immunité dans les infections à trypanosomes. [**Study of Immunity in Trypanosome Infections.**] —*Ann. Soc. Belge de Méd. Trop.* 1929. June 30. Vol. 9. No. 2. pp. 159–178. [24 refs.] [Bact. Inst., Louvain.]

After a brief review of the work of others on the subject of immunity in trypanosome infections, the author passes to his own investigations which relate especially to cross immunization and the Rieckenberg test. He used a strain of *T. pecaudi* which, as the result of numerous passages through mice, had acquired a considerable degree of virulence, killing the mice in 4 to 6 days.

The following are the conclusions:—

1. The immunity which results from the treatment of animals infected with the normal strain of trypanosomes is active only against this strain and not against the serum-resistant variety of it. Nevertheless, when the latter is transferred to a new animal, it loses its resistance to the immune substance and behaves in the cross immunity test differently to the normal strain. In fact, if it is true that animals immune to the normal strain are resistant to this strain and the resistant strain passed through a new

animal, normal animals cured of an infection of the resistant strain are only immune to this resistant strain previously passed through a new animal and not against the normal strain. In other words, the strain *pecaudi* rendered resistant to serum conserves its properties entirely only in so far as it is maintained in contact with the antibody which has caused its transformation.

Observations with the cross immunity experiments and with those of the Rieckenberg test performed with the strain resistant to serum which has been passed five times through new animals have given the same results as those obtained after a single passage of the serum-fast strain through a new animal.

These results differ from those obtained by Ehrlich and his school, and must, failing proof to the contrary, be attributed to the different species of trypanosome used.

2. *T. pecaudi* passed through another species of animal does not undergo any transformation appreciable by the cross immunity or Rieckenberg tests. Kroð's results, which differ from these, are also to be explained on the ground that he used a different species of trypanosome (*T. brucei*).

3. Comparative study of immunity *in vivo* and of Rieckenberg's test shows that the two may exhibit a certain discordance. It was found that trypanosomes resistant to serum passed through a new animal no longer infect animals resistant to the normal strain, and yet these trypanosomes behave differently in Rieckenberg's test from those of the normal strain.

4. In the phenomenon of attachment it is not only the platelets of the immune animal which produce the reaction ; when the test is performed with immune serum and citrated trypanosome blood, the test is equally positive.

5. Thrombocytobarins are formed in the course of an infection with *T. pecaudi* ; it was observed that the serum of animals in the last stage of infection causes attachment of the platelets to the trypanosomes obtained from the animal at the beginning of its infection.

It is not possible to explain with certainty the reason of this paradoxical phenomenon, particularly the absence of attachment of the platelets to the trypanosomes during infection, since these trypanosomes behave in cross immunity tests exactly as do those of the original strain.

W. Y.

Jamot (E.). La maladie du sommeil au Cameroun. [**Sleeping Sickness in Cameroon.**]—*Rev. Prat. Malad. des Pays Chauds.* 1929. July. Year 8. Vol. 9. No. 7. pp. 326, 329–332, 335–337.

In this article, which is of a general nature, the author gives a brief account of the history and present position of sleeping sickness in the Cameroons. No special reference is necessary.

W. Y.

i. Steudel. Die Schlafkrankheit und der Volkerbund. [**Sleeping Sickness and the League of Nations.**]—Reprinted from *Koloniale Rundschau.* 1929. No. 5. 7 pp.

ii. ——. Die Schlafkrankheit in Deutsch-Ostafrika vom Beginn bis zur Gegenwart. [**Sleeping Sickness in German East Africa from the Beginning until the Present.**]—Reprinted from *Mitt. a.d. Deut. Schutzgebieten.* 1928/9. Vol. 36. No. 2. pp. 61–79. With 1 map in text.

iii. ——. Epidemiologische Betrachtungen ueber die Wege der Schlafkrankheit und ihre Ausbreitung durch den Weltkrieg. [**Epidemiological Observations on Sleeping Sickness and its Spread through the World War.**]—Reprinted from *Africa. Jl. Internat. Inst. of African Languages & Cultures.* 1929. Apr. Vol. 2. No. 2. pp. 105–128. English summary pp. 128–129.

These three articles are of a general nature and contain nothing new. They require no special reference.

W. Y.

Carpenter (G. D. H.). Sleeping Sickness. A Lecture delivered to the Uganda Branch of the British Medical Association on 7th June, 1929.—*Kenya & East African Med. Jl.* 1929. Aug. Vol. 6. No. 5. pp. 131–148.

Zavattari (Edoardo). I tripanosomi africani parassiti dell'uomo. Nuovi fatti e nuove ipotesi sulla loro individualità.—Reprinted from *Riv. Sci. Naturali "Natura."* 1929. Vol. 20. pp. 73–91. With 6 figs. [3 refs.] [Inst. of Comparative Anat. & Physiol., Univ., Pavia.]

RABIES: A REVIEW OF RECENT ARTICLES. XII.*

i. *Virus.*

Pirani[1] describes cases of rabies in Eritrea, in man, donkey, dog, cat, etc. In most cases Negri bodies were not found in the brain, but experimental transmission was invariably successful. The clinical manifestations varied with the species of the animal, and with the number and position of the bites.

Levaditi, Lépine and Schoen[2] have continued their researches on the mutation of rabies virus. During the course of subpassage of a strain of street virus through two different series of animals they observed striking differences of character. The first series behaved in the usual manner and was progressively mutable into fixed virus, with decrease in the number of Negri bodies. In the second series the incubation periods were shorter (4, 5, 6 and rarely 7 days during 34 passages) and in none of the passages were Negri bodies observed. However, in the interior of the nuclei of certain neurones certain round, irregular or oval hyperchromatic basophile bodies of a hyaline appearance were found. These appear to result from the fragmentary degeneration of the nuclear chromatin, and from aggregation of the fragments. They are found chiefly in the horn of Ammon, and the authors suggest that they be called "intranuclear rabies bodies." This strain is considered to be a peculiar variety of fixed virus.

Nicolau and Kopciowska[3] have studied a virus DK submitted to them as a herpetic virus. It killed rabbits in 12 days when inoculated into the cornea. It seldom affected rabbits when rubbed into scarified skin. It killed in 4 to 7 days, with symptoms of paralysis when introduced intracerebrally. It had in general the characteristics of a fixed rabies virus. From a series of cross immunity experiments they conclude that the virus DK is a true rabies virus.

Remlinger and Bailly[4] contrast the viruses of rabies and herpes. The latter virus when inoculated into the brain remains localized at the site of inoculation as can be shown by animal experiment. The virus of rabies on the other hand disappears after some hours from the tissue at the point of inoculation. For several days it is absent, and then shortly before the first symptoms of the disease appears in control

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* For the eleventh of this series see Vol. 26, pp. 725–739.

[1] Pirani (Armando). Sulla lotta antirabbica in Colonia Eritrea.—*Arch. Ital. Sci. Med. Colon.* 1929. June 1. Vol. 10. No. 6. pp. 242–247. English summary p. 247. [Sero-Vaccine Inst. of Eritrea, Asmara.]

[2] Levaditi (C.), Lépine (P.) & Schoen (R.). Mutation brusque du virus rabique des rues en une variété particulière de virus fixe.—*C.R. Soc. Biol.* 1929. Aug. 13. Vol. 101. No. 25. pp. 1050–1057. With 4 text figs. & 2 graphs. [1 ref.]

[3] Nicolau (S.) & Kopciowska (L.). Identification d'un virus prétendu herpétique, en réalité rabique, par des expériences d'immunité croisée avec la rage. Immunisation anti-rabique cutanée, à l'aide d'injections intradermiques répétées de virus formolé.—*C.R. Soc. Biol.* 1929. June 28. Vol. 101. No. 22. pp. 655–657. [5 refs.]

[4] Remlinger (P.) & Bailly (J.). Sur une différence de comportement des virus rabique et herpétique dans l'encéphale du lapin.—*C.R. Soc. Biol.* 1929. July 5. Vol. 101. No. 23. pp. 773–775. [1 ref.] [Pasteur Inst., Morocco.]

animals, it reappears again. This suggests to the authors that the parasite of rabies has a cyclic development, whereas the agent of herpes has no cycle of evolution. The observation is considered to be in favour of the microspiridial character of the rabies parasite.

In a second communication REMLINGER and BAILLY[5] state that the rabies virus persists in the brain of the toad for not more than 3 days, in the frog for not more than 6 days, but in the tortoise for at least 54 days. Two explanations are suggested. The first that the duration of persistence is proportional to the volume of emulsion which can be inoculated (toad 0·2 cc., frog 0·3 cc., tortoise 0·5 cc.). The second is that if the virus of rabies is a microspiridion with a cyclic evolution, the virus may be able to carry out its cycle in receptive animals (rabbit) but not in refractory animals (tortoise).

In a third paper[6] these authors collect the evidence in favour of a cycle of evolution of the parasite. From experiments on the dog and the rabbit, which are receptive animals, it appears that the virus remains in situ at the point of inoculation and then disappears. This is called *the phenomenon of eclipse.* From experiments on refractory animals (tortoises) it appears that the virus can be recovered up to 110 days at the site of inoculation. This is called the *phenomenon of permanence.* In receptive animals they consider that the virus may have undergone cyclic evolution, whereas in the latter the cycle is interrupted.

TZEKHNOVITZER and GOLDENBERG[7] describe a curious property of the rabies virus. They find that whilst the serum of normal rabbits acts only feebly on atropine (0·4 cc. serum neutralizes 0·1 cc. of atropine 1/5000), the serum of the same rabbit 4 days after infection with fixed virus, neutralizes the same quantity of atropine in a dose of 0·0025 cc.

When the serum of the normal rabbit is more active (0·25 cc. neutralizes 0·1 cc. of atropine 1/500), the effect of inoculation with fixed virus is to neutralize the same quantity of atropine in a dose of 0·0006 cc. Thus the neutralizing power of the serum is augmented in both cases, in the first 160 to 320 times, in the second from 40 to 80 times. This action may be associated with the hyperactivity of the thyroid gland, of the hypophysis, and of the pineal gland induced during the course of rabies.

ii. *Symptoms.*

THIÉRY[8] draws attention to a case of a woman who died after having presented symptoms of rabies, and in whose brain Negri bodies were demonstrated. She had only been bitten on one occasion, and the dog in question, as to whose identity there was no doubt, survived without showing any symptoms of the disease. He examines the various hypotheses (1) that the dog was a carrier of the virus in a latent state, (2) that the woman had been previously bitten by another animal,

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[5] REMLINGER (P.) & BAILLY (J.). Sur le comportement du virus rabique dans l'encéphale de la tortue.—*C.R. Soc. Biol.* 1929. July 17. Vol. 101. No. 24. pp. 860–863. [Pasteur Inst. of Morocco, Tangiers.]

[6] REMLINGER (P.) & BAILLY (J.). L'évolution du parasite de la rage comporte-t-elle un cycle ?—*Ann. Inst. Pasteur.* 1929. Nov. Vol. 43. No. 11. pp. 1396–1407. [3 refs.]

[7] TZEKHNOVITZER (M.) & GOLDENBERG (J.). Propriété nouvelle du sérum des lapins infectés par le virus fixe.—*C.R. Soc. Biol.* 1929. Nov. 22. Vol. 102. No. 31. pp. 577–578.

[8] THIÉRY (J.). Un chien d'apparence saine peut-il transmettre la rage ?—*Rev. Gén. de Méd. Vét.* 1929. Aug. 15. Vol. 38. No. 452. pp. 451–460. [47 refs.]

(3) that the dog suffered from a mild type of infection followed by cure, and (4) that the dog was refractory to rabies, but had the virus in its saliva.

Knutti[9] describes a case of paralytic rabies, in which the course was that of an ascending paralysis of the Landry type. Negri bodies were found in the brain, and the animal test gave a positive result. The pathological changes found in the brain are described in detail.

iii. *Pathology.*

Ionnesco and Teodosiu[10] have estimated the glycogen content of fresh organs in cases of street and fixed virus rabies, employing the method of Best (after Schmorl). Glycogen was found in large quantity in the medulla, in various parts of the cerebrum, and in the horn of Ammon, both in street virus dog brains, and in fixed virus rabbit brains. Glycogen appears in the form of drops measuring from 3 to 4 μ. They occur in the protoplasm of large cells, or around the nuclei of small cells, and are also seen in the polynuclears and in endothelial cells. Glycogen is also found in the secreting cells of the kidneys, and in the heart.

Dwijkoff and Bogoslowskij[11] summarize the results of the post-mortem examination of the brains of 42 cases of human lyssa, within the period 1921–1927, at the Metschnikoff Institute at Moscow. In 38 of these (i.e., 90·5 per cent.), Negri bodies were found. In the remaining 4 the bodies were not found, and in these cases it is stated that the incubation period was short (15–20 days). As the incubation period becomes longer so does the number of bodies increase. In cases of short incubation the bodies are small structures, and as incubation lengthens they increase in size and in complexity of structure. The authors noted, however, cases of very long incubation with few bodies, and cases of short incubation with numerous bodies.

Ssawatejew and Ssidorow[12] divide Negri bodies into 5 types. The first and commonest is in the form of a rosette. A second type is ring-shaped. A third is characterised by "innen Korper." A fourth consists of elongated bodies containing small granules. A fifth type is of larger size. The staining method used is that of Carpano, after fixation by Schaudinn's method. From their observations the authors believe that the Negri body is not a cell degeneration, but a true parasite, which possibly has a cyclic evolution.

In a beautifully illustrated paper Tupa[13] describes modifications of

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[9] Knutti (Ralph E.). Acute Ascending Paralysis and Myelitis due to the Virus of Rabies.—*Jl. Amer. Med. Assoc.* 1929. Sept. 7. Vol. 93. No. 10. pp. 754–758. With 4 text figs. [23 refs.] [Med. School, Vanderbilt Univ., Nashville, Tenn.]

[10] Ionnesco (Démètre) & Teodosiu (T.). Le glycogène dans la rage.—*C.R. Soc. Biol.* 1929. May 31. Vol. 101. No. 18. pp. 321–322.

[11] Dwijkoff (P. P.) & Bogoslowskij (W. N.). Ueber die Negrischen Körperchen beim Menschen. Professor S. W. Korschun zum 35-jährigen Jubiläum seiner wissenschaftlich-ärztlichen Tätigkeit gewidmet.—*Zent. f. Bakt.* I. Abt. Orig. 1929. June 28. Vol. 112. No. 6/8. pp. 441–444. [4 refs.] ["Metschnikoff" Inst. for Infectious Diseases, Moscow.]

[12] Ssawatejew (A. I.) & Ssidorow (N. W.). Zur Morphologie der Negrischen Körperchen.—*Zent. f. Bakt.* I. Abt. Orig. 1929. Aug. 21. Vol. 113. No. 5/6. pp. 425–428. With 65 figs. on 1 double plate. [7 refs.] [Metschnikoff Inst., & State Inst. for Exper. Vet. Med., Moscow.]

[13] Tupa (A.). Recherches cytologiques dans la rage expérimentale.—*Arch. Roumaines Path. Expérim. et Microbiol.* Paris. 1929. Mar. Vol. 2. No. 1. pp. 113–128. With 36 figs. on 17 plates. [22 refs.] [Serolog. Inst., Bucharest.]

the mitochondria, and the internal apparatus of Golgi in the nerve cells of rabbits infected with fixed virus. The changes are described in detail, and can only be indicated here. The mitochondrial rods are elongated and their general arrangement is different to that found in the normal cell. The appearance suggests a dissolution of the constituents into the protoplasm rendering it more opaque. At the same time the mitochondria lose their staining properties. The terminal masses are augmented in volume to double or triple their normal size.

The internal reticular apparatus of Golgi shows similar changes, the " cordons " are unequal, irregular and vesiculated. The central parts lose their staining properties. In both instances the changes appear to be of an unknown physico-chemical nature. The apparatus of Golgi is partly hypertrophied, the mitochondrial arrangement is altered in direction and curvature, and the Nissl bodies are fragmented.

Koch[14] considers with special reference to three cases of human rabies in persons who had undergone pasteurian treatment, the possibility of determining whether the fixed virus of the vaccine or the street virus of the infection was the cause of death. Following Busson he holds that there is no sharp boundary between the two types of virus. The length of the incubation period is not a criterion : it may be short in cases of street virus infection, and long where fixed virus is operating. The type of animal employed for the test, the method of application, the quantity of vaccinal material, and various physical and chemical modifications all have their influence. In the three cases of paralytic and atypical human rabies which he describes such a differentiation was impossible. The virus appeared to be unevenly distributed in the various parts of the brain, and in some parts it was entirely absent. In practice, therefore, it would be necessary to carry out animal experiments with tissue from many parts of the brain and cord. He believes that treatment should be given to persons suffering from tuberculosis of the lungs only when it is absolutely necessary, since that disease predisposes the patient to street virus infection in an abortive paralytic form.

Busson[15] discusses the etiology of post-vaccinal paralysis. In a previous paper (this *Bulletin*, Vol. 26, p. 216), it will be remembered that he found fixed virus in the brains of two persons who had been inoculated with living virus but who had not come in contact with street virus. This strengthens his view that the cause of post-vaccinal paralysis is to be found in fixed virus. He believes that the essential difference between fixed virus and street virus lies in greater toxicity and greater " organo-specific fixation " with loss of general infectivity. He also holds the view that under certain conditions fixed virus can, to a certain extent, revert to the street virus type and so give rise to post-vaccinal paralysis. Amongst these conditions may be the introduction of a subsequent street virus infection or injury to the brain from other diseases such as tuberculosis.

The article is very closely reasoned and worthy of careful study.

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[14]Koch (Jos.). Kann die Differentialdiagnose, ob der Tod eines während oder nach der Pasteurschen Schutzimpfung gestorbenen Patienten durch das Strassen- oder Passagevirus verursacht wurde, durch den Tierversuch gestellt werden ? Ein Beitrag zur Klinik und Pathologie der paralytischen und atypischen Lyssa humana.—*Zent. f. Bakt.* I. Abt. Orig. 1929. Aug. 21. Vol. 113. No. 5/6. pp. 376–392. [30 refs.] [Robert Koch Inst., Berlin.]

[15]Busson (B.). Experimentelle Studien ueber das Lyssa-Virus.—*Zent. f. Bakt.* I. Abt. Orig. 1929. July 30. Vol. 113. No. 3/4. pp. 290–301.

Calderini[16] surveys in detail the whole question of the nocuousness of fixed virus. He also discusses the cases of Quast and Busson with reference to the presence of fixed virus in the brains of persons who have received antirabic treatment in which living fixed virus has been inoculated. He is of the opinion that as in certain cases the incubation period of street virus may be very short it is impossible to differentiate between the two varieties when both have gained access to the body.

The question whether fixed virus accumulates in the brains of individuals treated by living fixed virus, to which reference is made above and on many previous occasions, has been further studied by Isabolinski and Zeitlin.[17] Fifteen rabbits received a single subcutaneous dose of fixed virus brain (about 3·5 gm.), and were killed 7 to 14 days after this treatment. Two rabbits were inoculated with the brains of each of the 15. From 7 of the 15 original rabbits infection was conveyed to the test animals. Further subpassage proved that this was a true infection. In a second experiment on 10 rabbits active immunization by the Philips method was employed. In 4 of these the presence of rabies virus was proved by inoculation into further rabbits.

The authors conclude with Quast that there is an accumulation of virus in the brains of immunized rabbits.

Marie and Urbain[18] find that the serum of rabbits immunized against rabies contains antibodies. The cooked antigen of Kraus, Takaki and Michalka, in their hands appeared to possess no specific properties. On the other hand an unheated emulsion of the medulla of a rabid brain was an active specific antigen deviating 150 units, as compared with 30 units when normal or herpetic brain substance was used.

Gantt and Ponomarew[19] extend observations on the haemato-encephalic carrier previously referred to (this *Bulletin*, Vol. 24, p. 764 and Vol. 25, p. 191). Whilst the fixed virus of Leningrad does not ordinarily infect dogs even when given in large doses subcutaneously, intramuscularly or intravenously, and whilst dogs which have received similar doses of fixed virus followed by immediate extraction of 4 to 8 cc. of cerebro-spinal fluid, do not contract rabies, the authors have found that when the dose is given by the *intramuscular route*, followed by immediate removal of cerebro-spinal fluid, all the dogs so treated contracted the disease, their brains yielded fixed virus which could be subpassaged in rabbits. This result was obtained in an experiment in which 8 dogs were employed, 4 receiving subcutaneous doses, and 4 intramuscular doses into the muscles of the leg. In a confirmatory experiment, 6 dogs received doses introduced into the muscles of the

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[16] Calderini (M.). Il virus rabbico contenuto nel vaccino può arrivare ai centri nervosi nei vaccinati ?—*Giorn. di Batteriol. e Immunol.* 1929. Mar. Vol. 4. No. 3. pp. 216–235. [50 refs.]

[17] Isabolinski (M. P.) & Zeitlin (A. J.). Ueber die Speicherung des Virus fixe im Gehirn immunisierter Kaninchen.—*Ztschr. f. Immunitätsf. u. Experim. Therap.* 1929. Vol. 62. No. 3/4. pp. 233–237. [10 refs.] [State Bact Inst., Smolensk.]

[18] Marie (A. C.) & Urbain (Ach.). La réaction de fixation dans la rage.—*C.R. Soc. Biol.* 1929. June 21. Vol. 101. No. 21. pp. 561-563. [5 refs.]

[19] Gantt (W. Horsley) & Ponomarew (A. W.). Ueber den Mechanismus der Verbreitung des Tollwutvirus (Virus fixe) im Organismus.—*Ztschr. f. d. Gesamte Experim. Med.* 1929. Vol. 66. pp. 582–595. [25 refs.] [State Inst. for Exper. Med., Leningrad.]

shoulder : from 3 of these cerebro-spinal fluid was withdrawn on two occasions, all contracted rabies ; from the remaining 3 from which lymph fluid had not been withdrawn 1 died from another cause and the other 2 survived. It thus appears that for a successful infection with this strain of fixed virus, the injection must be intramuscular, and cerebro-spinal fluid must be removed. The first condition depends upon the richness in nerve endings. The second indicates that the removal of cerebro-spinal fluid facilitates the penetration of the virus into the central nervous system. In a further experiment the dose of virus was administered intravenously, and in this case the withdrawal of cerebro-spinal fluid appeared to have no influence. None of the dogs—whether the cerebro-spinal fluid was withdrawn or not—contracted the disease. Thus clearly the virus is carried to the central nervous system along the nerve trunks and apparently the withdrawal of fluid facilitated its progress. The authors failed to demonstrate this effect when the dose was injected into the larger nerve trunks (sciatic and brachial). In a further experiment, however, in which the nerve trunk was cut across, and the virus was applied to the cut surface the effect was clearly demonstrated, and the authors conclude that in the first instance the virus had not reached the axis cylinders. Thus finally the transmission of the virus is by the path of the axis cylinders of the nerves, and this transmission is facilitated by circumstances which increase the lymph flow within the nerve trunks. The authors suggest that this secondary action of the lymph fluid may operate in certain treated cases, and conditions may be such that fixed virus finds its way during treatment into the central nervous system. It is possible that this phenomenon may be related to the paralytic accident.

Remlinger and Bailly[20] present two cases which support Levaditi's conception of the existence of "*neuro-infections mortelles autosterilizable*" (this *Bulletin*, Vol. 26, p. 217). The first is that of a cock infected with street virus and dying of rabies. Negri bodies were found in the brain but the animal test was negative. The second also a cock ; an experimental infection with street virus : death on the 12th day : Negri bodies in brain : animal test negative.

Takaya[21] has examined the blood of persons treated by Kyoto's method with the following results : increase of transitional, large mononuclear and plasma cells : large increase of eosinophils : considerable increase of polynuclears : slight increase of lymphocytes : no change in the number of red blood cells. The most marked change is in the eosinophils.

Carvalho,[22] as the result of the examination of the blood of 100 persons, treated during 21 days with cords dried from four to one days, and examined on five occasions, finds the usual slight modifications in the percentage of the various cellular constituents ; i.e., lymphocytes

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[20]Remlinger (P.) & Bailly (J.). La rage et les neuro-infections mortelles auto-stérilisables.—*C.R. Soc. Biol.* 1929. Oct. 25. Vol. 102. No. 27. pp. 296–299. [3 refs.] [Pasteur Inst. of Morocco, Tangiers.]

[21]Takaya (Y.). L'influence de l'injection rabique sur l'état hematologique.—*Oriental Jl. Dis. Infants.* 1929. July. Vol. 6. No. 1. [In Japanese. French summary p. 17.] [Pediat. Inst., Imperial Univ., Kyoto.]

[22]Carvalho (M. Gonçalves). Labrocytose et image d'Arneth chez les individus soumis au traitement antirabique.—*Arquivos Inst. Bact. Camara Pestana.* 1928. Vol. 6. No. 1. pp. 22–41. [13 refs.] [Camara Pestana Inst., Lisbon.]

return to normal after some reduction, monocytes change in proportion to the lymphocytes, neutrophiles are reduced and later increase, eosinophiles augment constantly, basophiles remain in normal proportions. The Arneth count gives no indications which would form a guide to treatment.

In the French summary of a paper in Japanese by SEKI[23] it is stated that rabbits which have received an injection of benzol sufficient to cause a leucopenia, are more susceptible to rabies than are controls: that the effect of congestion by ligature of the jugular vein does not influence susceptibility: that the effect of anaemia by ligature of the carotid arteries is likewise ineffective.

iv. *Methods of Treatment and Statistics.*

HARRIS[24] reviews his experience at St. Louis, United States of America, of desiccated vaccines. He found that when the vaccine is frozen at —10° C. and dried in vacuo over sulphuric acid, about 2 per cent. of infectivity was preserved for several months. Fixed virus frozen with liquid air and then dried retained 90 per cent. of infectivity, and virus frozen with CO_2 snow and then dried as above retained 50 per cent. of its original infectivity. The subsequent loss of infectivity depends upon the temperature of storage. At a temperature of —1° C. virus retains infectivity up to three years. Subsequent experiments showed that a virus which had been preserved in vacuo until it became non-infectious, still possessed immunizing properties. In practice Harris gives 5 daily doses of 25 mgm. each of an old non-infectious vaccine, and follows with 5 similar injections of a strain partially attenuated over a period of 3 months. He quotes statistics of 3,516 cases, which includes one failure and one case of temporary post-vaccinal paralysis. For the prophylactic immunization of dogs he recommends an injection of a non-infectious vaccine, followed by a second injection of an attenuated but living virus.

D'AUNOY[25] relates his experience at New Orleans (U.S.A.) over a period of 18 years with Harris's vaccine. The virus is frozen with CO_2 snow, and dried over sulphuric acid or phosphoric anhydride in vacuo. The vaccine is stored at —12° C. to —18° C. in sealed tubes of pyrex glass. Dosage is measured in minimal infective doses. Such a dose being "the smallest quantity of desiccated material which within 5 days after preparation, and when kept at —12° C. to —15° C. will cause paresis in a 2,400 gm. rabbit within 7 days following intracerebral injection." The first dose consists of 250 "minimal infective doses," and the quantity is doubled daily until a maximum of 2,000 has been reached. An ordinary course consists of "11 treatments of 17,750 minimal infective doses." During the last 14 years 5,125 persons have been treated in this manner. Amongst these 5 have died from rabies, and 3 cases of paralytic accident (one fatal) have been observed.

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[23] SEKI (Yoiti). L'infection rabique dans ses rapports avec les troubles de la circulation.—*Oriental Jl. Dis Infants.* 1929. May. Vol. 5. No. 3. [In Japanese. French summary p. 32.] [Inst. of Pediat., Imperial Univ., Kyoto.]

[24] HARRIS (D. L.). Antirabic Immunization with Desiccated Vaccine.—*Amer. Jl. Public Health.* 1929. Sept. Vol. 19. No. 9. pp. 980–985. [3 refs.]

[25] D'AUNOY (Rigney). Antirabic Vaccination by Means of Desiccated Virus.—*Amer. Jl. Public Health.* 1929. Sept. Vol. 19. No. 9. pp. 986–990. [1 ref.] [Charity Hosp., Louisiana, New Orleans, La.]

The method of treatment used at Cluj (Romania) is peculiar. According to Botez and Albon[26] it consists of emulsions of dried cords along with emulsions heated according to the method of Piscariu, and preserved in neutral glycerine. Cords dried for from 0–4 days, are heated at 45°, 50°, 55° and 60°. The vaccine administered consists of various mixtures of unheated and heated vaccine to which emulsion of dried cords is added. Thus :—

Vaccine 0 :	emulsion unheated		+	emulsion of cord dried		0 days.
,, 1 :	,,	heated 45°+		,,	,,	1 day.
,, 2 :	,,	,, 50°+		,,	,,	2 days.
,, 3 :	,,	,, 55°+		,,	,,	3 days.
,, 4 :	,,	,, 60°+		,,	,,	4 days.

Treatment proceeds from vaccine 4 to vaccine 0, repeated according to the gravity of the case.

Estimations of the virulence of these vaccines show that the virulence of dried cords is variable. Vaccines 1–3 were virulent, but with prolonged incubation vaccine No. 4 was avirulent.

As the results from treatment by the method of Högyes as carried out at the Institute Alphonse XIII at Madrid were not satisfactory da Silva[27] has had recourse to etherized vaccines. As the number of persons to be treated is high (sometimes more than 250 daily) the methods of Alivisatos and Hempt have been slightly modified. The brain, divided into 4 parts, is placed in ether for 90 hours, it is then removed, and the ether is allowed to evaporate off under sterile conditions. The brain substance is then titrated, and physiological salt solution gradually added until an emulsion of 1 in 20 is obtained. This is then filtered through sterile gauze. Injections are carried out at single daily sittings, the dose for adults being 5 cc., and that for children 2 to 3 cc. Thirty injections are given in severe cases ; and 20 to the lightly bitten. So far only one failure has occurred amongst 1,158 persons treated.

The blood of 30 treated persons has been examined for the presence of rabicidal substances. These appear as a rule after the third injection, though in certain instances they may not appear until later. Their persistance depends upon the number of doses which have been given. These results are better than those of Alivisatos, who was unable to demonstrate the presence of rabicidal substances in the blood of individuals who had received less than 50 cc. during 15 days. Thus the author considers that his simpler method of preparation is more efficacious. Two cases of paralytic accident have occurred, one of which had a fatal issue. No rabicidal substances were found in the blood of 10 persons treated by the method of Högyes.

Fermi[28] gives the results of ten experiments in which mice or rats previously infected—one set with fixed virus, and one with street virus—were treated, some by Fermi's phenol vaccine, and others by the Phillips method.

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[26]Botez (M. A.) & Albon (T. V.). La virulence du vaccin employé à l'Institut antirabique de Cluj.—*C.R. Soc. Biol.* 1929. Oct. 18. Vol. 102. No. 26. pp. 187–188.

[27]da Silva (E. Pereira). Substances rabicides dans le sang des individus traités par le virus rabique fixe éthérisé.—*Arquivos Inst. Bact. Camara Pestana.* 1928. Vol. 6. No. 1. pp. 42–64. [12 refs.]

[28]Fermi (Claudio). Metodi di cura antirabbica Fermi e Phillips.—*Policlinico.* Sez. Prat. 1929. June 24. Vol. 36. No. 25. pp. 886–889. [3 refs.]

The proportions of survivors were as follows :—

	Infected with fixed virus.		*Infected with street virus.*	
	Treated with phenol vaccine.	Treated with glycerine vaccine.	Treated with phenol vaccine.	Treated with glycerine vaccine.
Dose : Experiment 1 ...	3 : 5	2 : 5	4 : 5	3 : 5
„ 2 ...	3 : 5	2 : 5	4 : 5	2 : 5
„ 3 ...	3 : 5	3 : 5	4 : 5	3 : 5
„ 4 ...	—	—	4 : 5	3 : 5
„ 5 ...	—	—	6 : 10	4 : 10
„ 6 ...	—	—	4 : 5	3 : 5
„ 7 ...	7 : 10	4 : 10	—	—
„ 8 ...	—	—	8 : 10	5 : 10
„ 9 ...	6 : 10	4 : 10	—	—
„ 10 ...	—	—	8 : 10	6 : 10
Totals	22 : 35	15 : 35	42 : 55	29 : 55

from which FERMI concludes that his treatment is more efficacious than that of PHILLIPS.

[The surprising uniformity in each column is perhaps worthy of note. It is not usual in experiments of this type to attain to such a degree of precision, though of course uniform series such as these will occur occasionally from random causes. This only emphasizes the general fact that when small numbers are employed the unusual event will occasionally turn up as the result of mere chance, and that quite wrong conclusions may occasionally be drawn from comparative experiments, simply because such comparative experiments happen by mere accident to have produced a very unusual distribution. On purely statistical grounds and according to the ordinary statistical arguments if there was no advantage in Fermi's method, such totals as he obtains would be expected to occur once in 10 times in the fixed virus series, and once in 100 times in the street virus series. The first result is not significant, and the second result *is* significant. Clearly further experiment is necessary.]

FERMI[29] also quotes a series of experiments carried out in 1907 (*Zeit. für Hygiene*, 1907), showing that treatment with 15 cc. of vaccine over a period of 30 days is much more efficacious than treatment with 30 cc. over a period of 6 days ; and again that treatment with 50 cc. over 30 days is more efficacious than with 50 cc. over 6 days.

GLOSTER, BEER, NAMBIAR and SASTRY[30] in an endeavour to compare the relative immunizing properties of carbolized vaccine (SEMPLE) and ether vaccine (ALIVISATOS) have arrived at the following results from experiments on animals.

[29]FERMI (Claudio). Sull'efficacia delle vaccinazioni antirabbiche intensive, abbreviate e prolungate.—*Policlinico.* Sez. Prat. 1929. Aug. 5. Vol. 36. No. 31. pp. 1103–1104. [4 refs.]

[30]GLOSTER (T. H.), BEER (W. A.), NAMBIAR (M. Raman) & SASTRY (S. Sitarama). Experiments on Pre-Infectional Immunization against Rabies with Carbolized and Etherized Vaccines.—*Indian Jl. Med. Res.* 1929. July. Vol. 17. No. 1. pp. 286–296. With 4 charts. [9 refs.] [Pasteur Inst. of Southern India, Coonoor.]

Three separate experiments were carried out, in which carbolized fixed virus was administered to guineapigs in doses proportional weight for weight to those used in the treatment of human beings, and the animals were tested by intramuscular injection of street virus given 17 to 25 days after the completion of treatment. The combined result is as follows. Of 116 untreated control animals, 92 succumbed to rabies (79·3 per cent.), whilst of 117 treated animals 36 died (30·7 per cent.)—a very significant result.

In one experiment on guineapigs etherized and carbolized vaccines were compared, the doses of the former being proportionate weight for weight to those given to human beings by ALIVISATOS, and the doses of the latter similarly proportional to those given to human beings in India. The test dose in each case was an intramuscular injection of a polyvalent street virus. The result was as follows :—

	Number of animals tested.	Deaths.	Percentage mortality.
Ether vaccine	22	0	0
Carbolized vaccine	24	7	29
Untreated	25	15	60

A modified experiment was carried out on rabbits. In this case the two vaccines were prepared from the same fixed virus brains. The doses contained the same proportion per body weight of nerve material and were given according to ALIVISATOS' scheme. The test was by inoculation of street virus on the scarified cornea. The result was as follows :—

	Number of animals tested.	Deaths.	Percentage mortality.
Ether vaccine	21	9	43
Carbolized vaccine	25	16	64
Untreated	25	25	100

It is stated by the authors that the ether vaccine used in these two experiments "was dead or highly attenuated as it failed to infect guineapigs or rabbits when injected subdurally." For details of procedure the reader is referred to the original paper. The authors conclude (1) that "carbolised vaccine in doses proportionate to those used for human beings confers considerable protection to guineapigs against subsequent infection with rabies," and (2) that "guineapigs and rabbits immunized with etherized fixed virus by Alvisatos' method show a higher degree of immunity than is obtainable by immunization with carbolized fixed virus (Semple) even when the latter is given in the same quantity for weight as the etherized fixed virus." A collateral observation of considerable practical importance may also be quoted. Of 49 guineapigs treated with carbolized *rabbit* fixed virus vaccine 20 contracted rabies (41 per cent.) whilst of 47 treated with carbolized *sheep* fixed virus vaccine 28 succumbed from rabies (60 per cent.) and of 48 untreated controls similarly tested 43 died (90 per cent.).

[It has been thought advisable on account of the importance of the issues involved to examine the significance of the death rates in the various experiments. The results may be summarized as follows: (*a*) The differences between treated and controls have in each case a definite significance. (*b*) Ether vaccines administered in doses per kilo similar to those employed by ALIVISATOS are significantly superior to carbolized vaccines administered in doses per kilo similar to those employed in India. (*c*) When the doses of etherized and carbolized vaccines contain the same amount of brain substance per kilo of rabbit the mortalities do not differ significantly—in fact if one assumes that the treatments have equal efficacies a result such as that obtained would be expected to occur once in every seven experiments. (*d*) The apparent superiority of rabbit fixed virus over sheep fixed virus is probably insignificant. Assuming that the two viruses are of equal efficacy, a similar result to that obtained would be expected to occur once in 15 times. As the criterion of significance generally adopted is " less than once in 20 times," it would be well if this experiment were repeated. (*e*) Finally, it appears that the efficacy of treatment by large doses of carbolized virus occupies a position somewhere between treatment by small doses of carbolized vaccine, and treatment by large doses of etherized vaccine. It is impossible from the available data to define this position more exactly.]

The statistics of the Pasteur Institute of Paris for the year 1928 are published by VIALA.[31] Of 671 persons treated, none developed rabies. No untoward incidents (paralytic or other) have been observed.

Statistics from the Institute of Experimental Medicine at Leningrad for the year 1928 are published by OUCHAKOV.[32] Of 1,106 persons treated, 1 died (0·09 per cent.). The vaccine employed is that of Fermi. It has also been distributed to 15 subordinate dispensaries. At these 2,100 persons were treated, of whom two developed rabies (0·1 per cent.). Two cases of paralytic accident of slight severity were observed at Leningrad.

DARLING[33] states that 5,799 persons were bitten in the City of Detroit during 1928. It was possible to obtain accurate information regarding the 2,783 dogs which bit them. Of these 581 had been vaccinated, and 2,202 had not been vaccinated. Of the 581 vaccinated 3 were rabid (or 0·52 per cent.). Among the 2,202 unvaccinated 131 were rabid (or 5·94 per cent.). From this selected group the mortalities amongst the unvaccinated and vaccinated were as 11·4 to 1. The problem was approached from a somewhat different angle, and the resulting proportion of mortalities amongst the unvaccinated and vaccinated was 12·5 to 1. The two results are consistent. The method employed is not stated, but only a single injection was given.

v. *Rabies in Animals.*

VIANNA[34] describes a case of rabies in the water hog (*Hydrochoerus capybara*). This animal had been enclosed in a cage next to a mad

[31] VIALA (Jules). Les vaccinations antirabiques à l'Institut Pasteur en 1928.—*Ann. Inst. Pasteur.* 1929. May. Vol. 43. No. 5. pp. 668–672.

[32] OUCHAKOV (V. G.). Service antirabique de l'Institut de Médicine Expérimentale. (Rapport annuel pour l'année 1928.)—*Arch. Sci. Biol.* 1929. Vol. 29. No. 3. pp. 255–265. [In Russian. French summary p. 266.]

[33] DARLING, Jr. (George B.). Does Vaccination protect Dogs against Rabies?—*Amer. Jl. Public Health.* 1929. July. Vol. 19. No. 7. pp. 811–812.

[34] VIANNA (Miguelote). Un cas de rage chez le cabiai (*Hydrochoerus capybara* Linn.).—*C.R. Soc. Biol.* 1929. Nov. 4. Vol. 102. No. 28. p. 420. [Bios Inst., Nictheroy, Brazil.]

dog. The two animals were separated by a grille and could not bite each other. The water hog died of paralytic rabies, Negri bodies were found in its brain, and the animal test was positive.

De Souza[35] describes a curious epizootic in the State of Matto Grosso, Brazil, in which bovines are mainly affected. The epizootic was at first ascribed to various causes, but has now been identified as rabies both by the presence of Negri bodies and by animal experiment. The question of direct contagion from herbivore to herbivore is fully discussed in the light of previous observations but no definite conclusion has been arrived at.

Remlinger and Bailly[36] describe cases of street virus rabies in pigeons which have been infected experimentally. They deduce their results from experiments on 50 pigeons, 15 of which were successfully inoculated. The rabies was invariably of the paralytic type, the incubation period being 12–24 days.

Plantureux[37 & 38] discusses the whole question of the control of rabies, and advises preventive vaccination, destruction of stray dogs, and the segregation of bitten non-vaccinated dogs. He describes the various methods of prophylactic inoculation, and discusses the statistical results.

Hull[39] discusses the spread and control of rabies in the State of Illinois. During the year 1927–1928 more than 1,200 rabid dogs were encountered. The histories of 452 rabid dogs were studied. Eighteen of these had previously received prophylactic treatment. Ten of them developed rabies within one month after vaccination, and were apparently in the incubation stage of the disease when they were vaccinated. Three developed symptoms 3½ months after vaccination. He finds that the stray dog is the reservoir of infection, and advises strict control of this class of dog. The home dog should be vaccinated against the disease.

After discussing the general questions of diagnosis and prophylaxis of rabies in animals de Freitas[40] discusses the results of his experience in the State of Espirito Santo (Brazil). He finds that a period of negative phase lasting for from 25 to 30 days follows the prophylactic dose. Experiments to test the duration of immunity show that after 5 months the treated animal is immune to an intraocular dose of 0·2 cc. of a 10 per cent. emulsion of fixed virus. During the year 1927, 1,219 animals were vaccinated, and during the year 1928, 1,352 animals were treated. From the year 1925 when operations were commenced there has been a steady decline in the number of cases of rabies.

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[35]De Souza (Moacyr Alves). A raiva em bovinos no Estado de Matto Grosso. Epizootia de Rozario Oeste.—*Rev. Zootechnia e Veterinaria.* 1929. Vol. 15. No. 2/3. pp. 65–84.

[36]Remlinger (P.) & Bailly (J.). La rage expérimentale du pigeon.—*C.R. Soc. Biol.* 1929. Nov. 4. Vol. 102. No. 28. pp. 376–378. [Pasteur Inst. of Morocco, Tangiers.]

[37]Plantureux (E.). Sur la vaccination préventive des chiens et la prophylaxie de la rage.—*Rev. Vét. et Jl. de Méd. Vét.* 1929. Aug. Vol. 81. pp. 409–419. [6 refs.] [Pasteur Inst., Algiers.]

[38]Plantureux (E.). Prophylaxie de la rage et vaccination préventive des chiens.—*Rev. d'Hyg. et de Méd. Préventive.* 1929. July. Vol. 51. No. 7. pp. 483–488.

[39]Hull (Thomas G.). The Spread and Control of Rabies.—*Jl. Amer. Vet. Med. Assoc.* 1929. June. Vol. 74. New Ser. Vol. 27. No. 7. pp. 1047–1051.

[40]de Freitas (H. Blanc). A Raiva e sua prophylaxia pela vaccinação.—*Rev. Zootechnia e Veterinaria.* 1929. Vol. 15. No. 2/3. pp. 93–99.

Dos Santos[41] states that at Coimbre (Portugal) antirabic immunization of dogs according to the method of Umeno and Doi has been employed on more than 27,000 dogs. The effect of these operations has been to reduce the number of persons coming for treatment at the Pasteur Institutes at Lisbon and Coimbre. They have observed 7 cases of post-vaccinal paralyses (or 0·5 per 1,000) amongst the dogs so treated.

Plantureux[42] recommends his formol vaccine for the treatment of bitten dogs, as well as for prophylactic vaccination. Following the procedure described in a previous paper (this *Bulletin*, Vol. 24, p. 227) four injections of formol vaccine are given at weekly intervals. The individual doses given are 15 cc. for animals between 3 and 7 kg., 20 cc. for dogs between 7 and 20 kg., and so on up to 70 cc. for animals between 225 and 300 kg. This method has been tested on dogs and sheep with success.

A paper by Herrmann[43] carries to a further stage a controversy between the author and Miessner and Baars. The former stated (this *Bulletin*, Vol. 25, p. 714), that a single dose of fixed virus, as large as it was safe to administer without risk of conveying infection, failed to give adequate protection. The latter claim that single safe doses of " Lyssin " are protective to dogs (this *Bulletin*, Vol. 26, p. 225). Herrmann from further experiments concludes that the maximum harmless dose of Miessner and Baars is insufficient to protect against subdural injection of a weak strain of street virus, and abides by his decision that a single subcutaneous dose of fixed virus does not give adequate protection.

A. G. McKendrick.

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[41]Dos Santos (Marques). La vaccination anti-rabique des chiens au Portugal. —*C.R. Soc. Biol.* 1929. June 7. Vol. 101. No. 19. pp. 390–391.

[42]Plantureux (E.). Traitement des animaux après morsure par le vaccin antirabique formolé.—*Bull. Acad. Vét. de France.* Paris. 1929. May. Vol. 2. No. 5. pp. 156–160. [1 ref.]

[43]Herrmann (O.). Ueber einmalige obligatorische Schutzimpfung der Hunde gegen Tollwut. II. Mitteilung: Entgegnung auf den Aufsatz von Miessner und Baars im Zentralbl. Bakt. Abt. I. Orig. Bd. 108, H.7/8.—*Zent. f. Bakt.* I. Abt. Orig. 1929. May 28. Vol. 112. No. 3/4. pp. 312–319. [12 refs.] [State Inst. for Med. Research, Kasan.]

REVIEWS AND NOTICES.

CHANDLER (Asa C.) [M.Sc., Ph.D., Professor of Biology, Rice Institute, Houston, Texas, recently Officer-in-Charge, Hookworm Research Laboratory, School of Tropical Medicine and Hygiene, Calcutta, India]. **Hookworm Disease. Its Distribution, Biology, Epidemiology, Pathology, Diagnosis, Treatment and Control.**—pp. xii+494. With 33 text figs. & 6 maps. 1929. Macmillan & Co., Limited, St. Martin's Street, London. [21s.]

It is curious, as the author of this book points out in his preface, that there is no treatise in existence giving an adequate account of the important work done in recent years in connexion with the human hookworms. There has grown up an immense literature on the subject but, apart from some excellent résumés in the annual reports of the International Health Board, those interested—and all medical men in the tropics and subtropics must be interested in a parasite which is almost ubiquitous in its distribution—must refer to innumerable scattered reports and papers to acquire an adequate knowledge. The great majority of these papers has been summarized in the pages of this *Bulletin* and it is greatly to be regretted that not only does Dr. Chandler not even mention this fact in his text or in his list of references, but actually states that " only a small fraction of the work is available to the majority even of the special workers in the field." Even although most of those interested in hookworm disease have easy access to the pages of this *Bulletin*, there is no doubt that a connected and comprehensive account of hookworms and hookworm-disease will be of immense value.

This volume collects and collates the literature dealing with the distribution, structure, life cycle and bionomics of the parasite, the epidemiology, pathology, diagnosis, treatment, prevention and control of the disease and the technical methods employed in connexion with hookworms, their eggs and their larvae. It concludes with an extensive bibliography and a useful index.

The plan of the book is excellent and practically all the modern literature is surveyed within its pages. Each chapter, however, is written as though it were a separate article, almost unconnected with previous chapters, and there is much unnecessary repetition. Thus, for example, SVENSSON's experiments with larvae of different species of hookworms are summarized in some detail on page 92 and again on page 141—the main difference between the two accounts lying in the use of the Fahrenheit scale of temperature in the first and the Centigrade in the second. This indiscriminating mixing of the two temperature scales is, indeed, an irritating feature of the whole book.

In spite of these and other evidence of somewhat hasty preparation of the subject matter, the book is a valuable contribution to the literature of tropical diseases. It contains within its covers much material available only in scattered papers in many languages or in summaries in various numbers of this *Bulletin*, material which should be available to every tropical practitioner and a careful study of which would do much to clear up the many misconceptions still held about hookworms. The author, whose own contribution to this literature is no mean one, has rendered the subject a valuable service in bringing this material together.

T. W. M. Cameron.

FAUST (Ernest Carroll) [Ph.D., Professor of Parasitology in the College of Medicine of Tulane University, New Orleans, Louisiana]. **Human Helminthology. A Manual for Clinicians, Sanitarians and Medical Zoologists.**—pp. xxii+616. With 297 engravings. 1930. London : Henry Kimpton, 263 High Holborn, W.C. [36s.]

This is the first modern full-sized text book to deal exhaustively and exclusively with human helminthology : and it does so in such a way as to make it at once, one of the most important books of reference for all who have to deal with the human entozoa. The author is a well-known authority on parasitic helminths and his contributions to helminthology include some of the standard monographs on the subject. In addition, he has had unrivalled opportunities of studying and teaching in China—the land, *par excellence* of the parasitic worms, where, indeed, modern helminthology had its birthplace. When to these qualifications, one adds the gift of a clear, lucid style, the result is the production of a volume which will appeal alike to helminthologists, hygienists, and clinicians.

The plan of the book is simple. The first few chapters are devoted to general considerations, including an excellent résumé of the often imperfectly understood Rules of Zoological Nomenclature, and an annoted list of current literature. Then follows a discussion on the parasitic worms, their zoological, pathological, clinical, and sanitary aspects. Every helminth which has been reported from man is included and this feature marks the volume as a work of reference rather than a student's textbook. The fourth and last section discusses technique and includes lists of apparatus, methods of collecting and preparing specimens, means of identification and finally lists of intermediate and reservoir hosts : the last group is by no means as complete as it might be, however.

The book is copiously and excellently illustrated and a large proportion of the drawings are original. References to literature are appended to each chapter and are well selected to include the more important works.

There are relatively few misprints and fewer mistakes ; those that do occur are mostly minor ones. One important misprint, however, is the transposition of the words *Ancylostoma* and *Necator* on the map (on page 370) showing the distribution of the human hookworms : and on page 368, the author is in error in stating that the distal end of *each* of the spicules of *Necator* is provided with a delicate barb. (Actually, the two spicules fuse to form a single barb.) These are minor and easily corrected points, however, which are almost inevitable in a book of this magnitude.

Professor Faust has introduced no new species into this book, but he had made considerable alterations in classification and nomenclature. A number of new names are introduced and for medical readers the most important is the creation of a new genus *Mansonella* for the reception of "*Filaria*" *ozzardi*, originally described by Sir Patrick MANSON in 1897.

Professor Faust has to be congratulated on the production of an excellent piece of work, one which is not only of considerable academic interest, but which will prove of the utmost value to every student of parasitology in all its various aspects.

T. W. M. Cameron.

PEIPING UNION MEDICAL COLLEGE. **A Glossary of Bacteriological Terms (English-German-Chinese).**—144 pp. Issued by the Division of Bacteriology, Peiping Union Medical College, Peiping, China. [Received from the Peking Union Medical College, Peping.] [Review appears also in *Bulletin of Hygiene.*]

This Glossary places the English words first, and it is these which are in alphabetical order, even to the extent of such entries as "Preparation, unstained." It would seem therefore that the Glossary is intended to be

used by those who know German or Chinese and wish to read English writings, and considerable improvement could have been effected by having the English column revised by an English bacteriologist.

If a reviewer may make the suggestion without giving offence to those who speak and write a very ancient language, the adoption by China of the Roman alphabet would be of advantage to the scientists of that country no less than to those of western lands.

J. F. C. H.

HASLAM (J. F. C.) [M.C., M.D. (Edin.), M.R.C.P. (Edin.), D.P.H., Assistant Director, Bureau of Hygiene & Tropical Diseases; Director of Library Services, London School of Hygiene & Tropical Medicine; formerly Government Medical Officer of Health, British Guiana]. **Recent Advances in Preventive Medicine. With a Chapter on the Vitamins** by S. J. COWELL, M.A., M.B., M.R.C.P., Professor of Dietetics in the University of London.—pp. viii+328. With 30 illustrations. 1930. London: J. & A. Churchill, 40, Gloucester Place, Portman Square. [12s. 6d.] [Review appears also in *Bulletin of Hygiene*.]

The plan of Dr. Haslam's book is shown in the following extract from the Preface :—

" In the days of Chadwick, preventive medicine meant little more than what we now call sanitation, and twenty years ago, or less, it would have been proper to begin this book with an account of what was new regarding water supply, drainage and sewage disposal. Preventive medicine has come to mean something more extensive . . . The modern programme of preventive medicine has been admirably sketched by Sir George Newman in his ' Outline of the Practice of Preventive Medicine,' and this book attempts to use that ' Outline ' as a sort of framework round which to build a serviceable account of recent study of the problems of present-day preventive practice."

The modern outlook upon preventive medicine is sketched in an introductory chapter and the following chapters deal with recent work in most of the matters listed in NEWMAN'S " Provisional Articles of a National Policy in Preventive Medicine." The chapter titles indicate the scope of the book : Eugenics, Maternal Mortality, Wastage of Young Life, Childhood, Milk, Vitamins, Atmospheric Conditions, Hygiene in Industry, Active Immunization. Exhaustive treatment of any one of these subjects would, of course, fill a whole volume, but here attention has been restricted mainly to aspects of these subjects which have been acquiring special importance of late, but which, as yet, are but little noticed in standard text books. For example, the chapter entitled Hygiene in Industry, deals with industrial accidents, telegraphists' cramp, pulmonary asbestosis and sickness in the printing industry. The first of these includes the very interesting results obtained by GREENWOOD and WOODS and NEWBOLD, approaching the problem from the statistical side, and of FARMER and CHAMBERS who carried the research a stage further by psycho-physiological tests. The second also brings out the need for seeking the help of the psychologist as shown by May SMITH, CULPIN and FARMER. The third subject is a new disease entity in industrial pathology, and the fourth is a good example of the need (and difficulty) of arriving at exact knowledge of industrial morbidity as a prelude to elucidating causative factors.

Readers of the *Bulletin of Hygiene* will find here connected accounts of many of the matters which have formed the subjects of reviews and summaries published in its pages.

A. G. B.